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USE OF D4 AND 5-HT2A ANTAGONISTS, INVERSE AGONISTS OR PARTIAL
AGONISTS

Field of the invention

5 The invention relates to the field of neuropsychiatry. More specifically, the invention relates to the use of compounds, which have D4 and 5-HT2A antagonist, inverse agonist or partial agonist activity, for the preparation of medicaments.

Background of the invention

Conventionally, mental disorders are divided into types based on criteria sets with defining features. DSM-IV (*American Psychiatric Association*, (1993 – ISBN 0 – 89042 – 061 – 0))
10 is the in the art well-known golden standard of such a categorical classification. In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. Individuals sharing a diagnosis are likely to
15 be heterogeneous even in regard to the defining features of the diagnosis. Thus, the categorical defined mental disorders as mood and anxiety disorders are having an external and even internal variable co-incidence of symptoms concerning e.g. mood, anxiety, perception, feeding, somatic sensations, sexual functions, sleep, cognitive functioning, impulse control, attention, substance use, personality, bereavement, identity,
20 phase of life, abuse or neglect and other aspects of behavior.

In a dimensional system, clinical presentations are classified based on quantification of attributes i.e. dysfunctions rather than the assignment to categories and works best in describing phenomena that are distributed continuously and that do not have clear boundaries.

25 Emotion dysregulation is known as such an attribution or dysfunction that plays an important role in the development and course of mental disorders (*Gross, J. J. & Munoz, R. F.*, 1995, *Emotion regulation and mental health, Clinical Psychology: Science and Practice*, 2, 151-164; *Mennin, D.S., Heimberg, R. G., Turk, C. L. & Fresco, D. M.*, 2002, *Applying an emotion regulation framework to integrative approaches to generalized anxiety disorder, Clinical Psychology: Science and Practice*, 9, 85-90; *Linehan, M. M.*, 1993, *Cognitive-behavioral treatment of borderline personality disorder*, New York, The Guilford Press; *Gratz, K. L., Roemer, L.*, 2001 & 2004, *Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation*
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of the Difficulties in Emotion Regulation Scale, Annual meeting of the Association for Advancement of Behavior Therapy, Nov. 2001 & Journal of Psychopathology and Behavioral Assessment, Vol. 26, No. 1, March 2004) besides behavioural and cognitive dysfunctions. D4 dopamine receptors (D4DR), almost exclusively present in the mesocortical and mesolimbic systems (O'Malley, K. L., Harmon, S., Tang, L., Todd, R. D.,
5 The rat dopamine D4 receptor: sequence, gene structure, and demonstration of expression in the cardiovascular system, New Biol., 4, 137-46, 1992), are in the art known as modulators of emotion and cognition. D4DR agonistic activity gives a behavioural sensitisation; D4DR antagonistic activity leads to an emotion modulation (Svensson, T. H.,
10 Mathé, A. A., Monoaminergic Transmitter Systems, Biological Psychiatry (eds. D'Haenen, H., et al.), 45-66, 2002, John Wiley & Sons, Ltd). Data demonstrate that agonism of the dopamine D4 receptors play an important role in the induction of behavioral sensitization to amphetamine and accompanying adaptations in pre- and postsynaptic neural systems associated with the mesolimbocortical dopamine projections (D. L. Feldpausch et al.; The
15 Journal of Pharmacology and Experimental Therapeutics Vol. 286, Issue 1, 497-508, July 1998).

Results suggest that the antagonisms of cortical D2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher *in vivo* binding to the D2 receptors in the cortex than in the basal ganglia is suggested as an
20 indicator of favorable profile for a putative antipsychotic compound (X. Xiberas and J.L. Martinot; The British Journal of Psychiatry (2001) 179: 503-508). Results show that dopamine D4 receptor antagonism in the brain does not result in the same neurochemical consequences (increased dopamine metabolism or hyperprolactinemia) observed with typical neuroleptics (Smita Patel et al., The Journal of Pharmacology and Experimental
25 Therapeutics Vol. 283, Issue 2, 636-647, 1997). The selective D4 dopamine receptor antagonist L-745,870 was ineffective as an antipsychotic for the treatment of neuroleptic responsive patients with acute schizophrenia (Kramer, M.S. et al., Arch. Gen. Psychiatry 1997 Dec; 54(12):1080).

Finally, in the biological system, mental disorders are defined on other levels of
30 abstraction than in the categorical and dimensional system. Structural pathology (e.g. amyloid plaques in Alzheimer Disease), etiology (e.g. HIV Dementia) and deviance from a physiological norm (e.g. reduced cerebral blood flow) are often used as indicative biological markers for a mental disorder. The underlying dysregulation of various neurotransmitter systems (glutamatergic, GABAergic, cholinergic, monoaminergic (nor-adrenergic, dopaminergic, serotonergic), etc.) is the in the art used model for the
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explanation of the biological determinants of the clinical presentation of mental disturbances. It is known that the Serotonin 2A Receptor (5-HT_{2A} receptor) - which is widespread in the Central Nervous System (CNS) - has a regulating role on the dysregulation of various neuro-transmitter systems. 5-HT_{2A} agonism gives several behavioural disturbances; 5-HT_{2A} antagonism leads to a governance of mood, social behaviour, anxiety, cognitive function, stress, sleep functions, nociception, sexual functions, feeding and other aspects of behaviour (*J.E. Leysen (2004) 5-HT₂ Receptors; Current Drug Targets – CNS & Neurological Disorders, 2004, 3, 11-26*).

Dysregulation of the HPA axis (hypothalamic - pituitary - adrenal axis) has frequently been reported in patients with psychiatric disorders, and is among the most robustly demonstrated neurobiological changes among psychiatric patients (*D.A. Gutman and C.B. Nemeroff, Neuroendocrinology, Biological Psychiatry (eds D'Haenen, H., et al), 99, 2002, John Wiley & Sons, Ltd*). The resulting elevated plasma cortisol concentrations leads to an enhanced binding of serotonin for the 5-HT_{2A} receptor (*E. A. Young, Mineralocorticoid Receptor Function in Major Depression, Arch. Gen. Psychiatry, Jan 2003; 60: 24 - 28*) and thus agonism.

Additionally 5-HT_{2A} antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT_{2A} receptor on (i) the 5-HT_{1A} receptor stimulation by serotonin (*S. M. Stahl, Newer Antidepressants and Mood Stabilizers, Essential Psychopharmacology, 265, University Press; 2 edition (June 15, 2000); ISBN: 0521646154*) and on (ii) the dopamine release in the mesocortical systems (*S. M. Stahl, Classical Antidepressants, Serotonin Selective and Noradrenergic Reuptake Inhibitors, Essential Psychopharmacology, 233, University Press; 2 edition (June 15, 2000); ISBN: 0521646154*).

Clinical or real effectiveness of psychopharma is very rare via common pooping-out; many treatment-refractory patients and up to half of patients fail to attain remission (*S. M. Stahl, Essential Psychopharmacology, Depression and Bipolar Disorders, 151, University Press; 2 edition (June 15, 2000); ISBN: 0521646154*). Implications of not attaining remission for Mental Disorders are increased relapse rates, continuing functional impairment and increased suicide rate (*S. M. Stahl, Essential Psychopharmacology, Depression and Bipolar Disorders, 152, University Press; 2 edition (June 15, 2000); ISBN: 0521646154*). Clinical causes of not attaining remission by the Current Psychopharmacological Compounds are inadequate early treatment, underlying emotion dysregulation (affecting instability – hypersensitivity – hyperaesthesia – dissociative phenomena, etc.) and competitive antagonism. There is thus a growing need for a more efficient therapy and more efficient, selective and efficacious medicaments for treating mental disorders.

Summary of the invention

The present invention relates to the use of compounds and pharmaceutical compositions having D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity for the treatment of the underlying emotion dysregulation of mental disorders (e.g. affecting instability – hypersensitivity – hyperaesthesia – dissociative phenomena - etc.) and to methods entailing administering to a patient diagnosed as having a mental disorder a pharmaceutical composition containing (i) compounds having specific high selective D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity and (ii) a known medicinal compound and/or compositions of compounds. The combined D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic effects may reside within the same chemical or biological compound.

Taken into account the above mentioned (i) rare clinical or real effectiveness of psychotropics, (ii) the governance of the features and dysfunctions responsible - in a variable co-incidentally – for the clinical state of the mental disorders by D4 dopamine receptor (D4DR) and 2A serotonin receptor (5-HT2A) antagonism and (iii) the fact that 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (a) the 5-HT1A receptor stimulation by serotonin and on (b) the dopamine release in the mesocortical systems, the present invention relates to the use of a compound for the preparation of a medicament for treating a disease or disorder with an underlying emotion dysregulation, characterised in that said compound has (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors and wherein said compound is administered to a patient in a dose ranging between 5 and 15 mg of the active ingredient. Preferably, said compound is pipamperon.

In a preferred embodiment, in a mono therapeutic context, the invention relates to the use of a compound as defined above, preferably pipamperon, for preparing a medicament for treating a disease or disorder selected from the group comprising anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders,

personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

According to a further embodiment the invention relates to the use of a first compound as defined above for the preparation of a medicament for treating a mental disease or disorder with an underlying emotion dysregulation whereby a second compound is administered simultaneously with, separate from or sequential to said first compound to augment the therapeutic effect of said second compound on said disease, or to provide a faster onset of the therapeutic effect of said second compound on said disease.

The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders; (iii) pain disorders; and (iv) Parkinson Disease.

In a preferred embodiment, the first compound is administered daily at least one day before administering said second compound.

Preferably, said second compound is characterized by the physiological property of influencing positively the activity of the Central Nervous System.

The invention also relates to a method for preparing a compound having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist activity comprising the following steps: (a) measuring the selective affinity of a test compound to the D4 receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the D4 receptor in respect to all the other D receptors, and measuring the selective efficacy of the

- selected compound to the D4 receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the D4 receptor; (b) measuring the selective affinity of a test compound to the 5-HT2A receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the 5-HT2A receptor in respect to
- 5 all the other 5HT receptors, and measuring the selective efficacy of the selected compound to the 5-HT2A receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the 5-HT2A receptor; (c) identifying a compound which is selected in (a) and (b), (d) preparing the compound identified in (c).

The invention further also relates to a compound prepared by the described method.

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Detailed description of the invention

- The present inventors surprisingly found that compounds which have a high selective affinity towards the 5-HT2A receptor and which, at the same time have a high selective affinity towards the dopamine-4 (D4) receptor show an improved effect in treating
- 15 underlying emotion dysregulation of mental disorders.

The compounds according to the invention may be chemical or biological in nature, or may be chemically synthesised. Preferably, the compounds of the invention are provided as a pharmaceutically acceptable salt.

- One example of such a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors is pipamperon. Pipamperon is the conventional name given for the compound of the formula 1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide.
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- 25 Pipamperon is also the active ingredient of for instance the commercially available Dipiperon (Janssen, Cilag B.V).

- Further, the present inventors surprisingly found that the dosage of active ingredient for pipamperon in treatment (in monotherapy as well as in combination therapy as described in more detail further) could be very low compared to conventionally used dosages.
- 30 Preferred dosages which, according to the invention, have been shown to be effective for treating these mental disorders, range between 5 and 15 mg per day or between 5 and 10 mg per day. More preferably, dosages of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg per day are used in treatment of the diseases of the invention. In conventional pipamperon

treatment, the active ingredient is available in tablets of 40 mg per tablet or in solutions of 2 mg per drop. Conventional usage of high doses ranging from 40 to 360 mg is prescribed. For instance, for children up to the age of 14, doses corresponding with 2 to 6 mg per kg body weight are conventionally prescribed. The high selective affinity of pipamperon towards the 5-HT_{2A} receptor and the D₄ receptor is reflected in the low dosage which is needed for the treatment of the mental diseases listed below and also contributes to the efficacy of the treatment.

The mental disorders which can be treated using pipamperon in a mono therapy at such low doses are for instance anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

Mental disorders such as depression are commonly treated with serotonin re-uptake inhibitors. Unfortunately, however, these compounds can give rise to side effects in use. Moreover, a substantial problem in most treatment of mental disorders is the non-response to selective serotonin re-uptake inhibitors (SSRIs). Also the onset of the therapeutic effect can be delayed undesirable.

A problem to be solved by the present invention is thus the provision of a more efficient therapy and efficient, highly selective and efficacious medicaments for treating mental disorders.

The inventors found that, for instance, the non-response to selective serotonin re-uptake inhibitors (SSRIs) in depression may be declared by (partial) inhibition of the 5-HT_{1A} stimulation via 5-HT_{2A} stimulation. Des-inhibition thereof via 5-HT_{2A} antagonism seems to be an answer to this problem.

The present inventors found that a simultaneous or foregoing treatment with a compound having a high selective 5-HT_{2A} antagonist, inverse agonist or partial agonist activity, could lead to a greater response towards, for instance, SSRIs. However, not all compounds exhibiting 5-HT_{2A} antagonism are useful: competition between 5-HT_{2A} stimulation via serotonin and 5-HT_{2A} antagonism via the compound could be responsible for the lack of

more efficacy of compounds which have both a selective serotonin re-uptake inhibitory and 5-HT2A antagonist profile, such as trazodone and nefazodone.

5 The present inventors further surprisingly found that a simultaneous or foregoing treatment with a compound having a high selective D4 antagonist, inverse agonist or partial agonist activity in combination with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity could lead to a greater response towards, for instance, SSRIs, or any of the compounds listed in Table 6 or below. In addition, the inventors found that a combination treatment provides less residual symptoms and more remission relative to a mono therapy with these compounds.

10 As such, in a combination treatment, the doses of the compounds listed in Table 6 for treating patients with mental disorders may be decreased to about 10 - 90% of the conventional dose, preferably to about 20 - 80%, or 30 - 70%, or 40 - 60% or to about 50% of the conventional dose. Even if the administered dose of the compound is decreased in the combination therapy, the therapeutical effect may be sustained or
15 ameliorated relative to the conventional dose. The danger of side effects of a treatment with such compounds can be decreased or minimized in the combination therapy of the invention. In this regard, the term conventional dose refers to the dose used heretofor for a particular compound in treating patients with a mental disorder, for instance, according to the supplier's or physician's description or as listed in Table 6.

20 In this invention, the term "antagonist" refers to an interaction between chemicals in which one partially or completely inhibits the effect of the other, in particular agents having high affinity for a given receptor, but which do not activate this receptor.

In this invention, the term "inverse agonist" refers to a ligand which produces an effect opposite to that of the agonist by occupying the same receptor.

25 In this invention, the term "agonist" relates to an agent which both binds to a receptor and has an intrinsic effect.

In this invention, the term "partial agonist" relates to an agent with lower intrinsic activity than a full agonist, and which produces a lower maximum effect.

30 The present inventors found that a compound which binds to the 5-HT2A receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other 5HT receptors is less than 8 in combination with a high selective affinity for the D4 receptor, i.e. which bind to the D4 receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other dopamine receptors is less than 8 also show such an improved effect in treatment. These effects, i.e. D4 antagonism, inverse agonism or partial agonism and 5-

HT2A antagonism, inverse agonism or partial agonism, may reside in the same compound.

The term "other 5HT receptors" as used herein relate to for instance 5-HT1 receptors (e.g. 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F), 5-HT2B, 5-HT2C, 5-HT6 (rat) and 5-HT7 (rat).

By the expression "selective affinity for the 5-HT2A receptor" is meant that the receptor has a higher affinity for the 5-HT2A receptor than for other 5-HT receptors.

The expression "selective affinity for the D4 receptor" means that the receptor has a higher affinity for the dopamine D4 receptor than for other dopamine receptors.

10 The term "other dopamine receptors" are, for instance, D1, D2 and D3 dopamine receptors.

pKi values of test compounds for dopamine receptors as well as 5-HT2A receptors can be measured using commonly known assays.

15 Compounds which have a selective affinity for the D4 receptor preferably have a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors.

Preferably, the compounds of the invention which have a selective affinity for the 5-HT2A receptor (or the D4 receptor), are compounds which have a pKi value equal to or higher than 8 towards the 5-HT2A receptor and the D4 receptor, and less than 8 towards other 5-HT receptors or dopamine receptors, respectively, as can be measured, for instance by methods known in the art. For instance, the "NIMH Psychoactive Drug Screening Program (PDSP)" K_i database (<http://kidb.cwru.edu/nimh/5htp.php>), is a unique resource in the public domain which provides information on the abilities of drugs to interact with an expanding number of molecular targets. The PDSP K_i database serves as a data warehouse for published and internally-derived pKi, or affinity, values for a large number of drugs and drug candidates at an expanding number of G-protein coupled receptors, ion channels, transporters and enzymes. The PDSP internet site also provides for commonly used protocols and assays for measuring pKi values of 5-HT and dopamine receptors.

25 A preferred example of a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other

Dopamine receptors and which is therefore useful in a combination therapy is pipamperon.

Table 1 illustrates the selective affinity of for instance pipamperon for the 5-HT_{2A} and for the D₄ receptor. In addition, Table 1 also illustrates the low or absence of affinity of
5 pipamperon for other receptors such as the adrenergic receptors Alpha 1A, Alpha 2A, Alpha 2B, Alpha 2C, Beta 1, Beta 2, and the histamine receptor H₁. As such, treating patients with pipamperon will provide for less side effects which otherwise result from simultaneous stimulation of other receptors. Therefore, and according to preferred
10 embodiments, useful compounds according to the invention not only have a selective 5-HT_{2A} and/or D₄ affinity but also a low affinity for other receptors such as the adrenergic and histamine receptors.

The low dosage which can be used in pipamperon treatment, as already described earlier, contributes to the high selective affinity of the compound towards the 5-HT_{2A} receptor and the D₄ receptor and therefore also to the efficacy of the treatment.

15 The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) the non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders,
20 adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive
25 diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive
30 impairment disorder, other cognitive disorders; (iii) the pain disorders; and (iv) Parkinson Disease. In Table 5, this classification has been used for summarizing the diseases and disorders relative to known psychotropics. In Table 6, an overview of pharmacological grouping is provided, indicating the pharmacological profile numbering, the pharmacological profile, the main disease or disorder indication(s), the name of the compound, the dose
35 range, and the company producing or selling said compound.

These diseases and their diagnosis are very clearly defined in the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" published by the American Psychiatric Association. This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of mental disorders and is commonly used in the field of neuropsychiatry. It is for instance available on the internet under:

<http://www.behavenet.com/capsules/disorders/dsm4tr.htm>.

The expression "non-cognitive diseases or disorders" used in some of the embodiments of the invention comprises the following group of diseases or disorders: mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect.

In other embodiments of the invention, the mental diseases or disorders that are characterized by an underlying emotion dysregulation belong to the group of pain disorders. For instance, the combination therapy with pipamperon is especially advantageous for management of acute pain in diseases such as, but not limited to, musculoskeletal diseases, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. For the classification of pain disorders, reference is also made to the DSM-IV where these disorders are clearly described in the section of somatoform disorders by way of internationally accepted diagnostic criteria.

In other embodiments of the invention, the 5-HT_{2A} receptor and/or Dopamine-4 receptor antagonist, inverse agonist or partial agonist (e.g. pipamperon) is used in treatment of patients having neuro-degenerative diseases or disorders, or related cognitive diseases or disorders. The diseases or disorders of the present invention are characterized by an underlying degeneration of the Central Nervous System (CNS), preferably selected from the group consisting of, but not limited to, neurodegenerative diseases such as Parkinson Disease, and in other embodiments of the invention, selected from the group of (related) cognitive diseases or disorders such as Alzheimer Disease.

For instance, Parkinson Disease, which is a chronic progressive nervous disease chiefly of later life, is linked to decreased dopamine production in the substantia nigra and is

marked by tremor and weakness of resting muscles and by a shuffling gait. Dopamine agonists and even levodopa, widely used in Parkinson Disease, gives via a dopamine D4 receptor stimulation psychiatric manifestations. The induced release of serotonin acts via 5-HT2A stimulation as a "brake" on dopamine release (Young B.K., Camicioli R., Ganzini L., *Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. Drugs Aging. 1997 May; 10(5): 367-83*). Because of the need of specific D4 and 5-HT2A antagonism in the treatment of Parkinson Disease with dopamine agonists and even levodopa, it seems reasonable to combine with a compound with a high selective D4 and 5-HT2A antagonism i.e. having merely no activity towards the other receptors especially the D2 receptor because of the primary need of the relieve of the excessive burden of remaining dopaminergic neurons. Therefore, the use of the so-called atypical anti-psychotics or serotonin-dopamine antagonists (SDAs) is absolutely contraindicated since their high affinity for the D2 receptor. Even the use of serotonin releasing compounds such as SSRIs in the absence of an effective 5-HT2A antagonism are contraproductive towards the Parkinson Disease symptoms although many Parkinson patients are in need for an antidepressant since major depression is a very common and disabling condition in this kind of patients.

The expression "(related) cognitive diseases or disorders" according to the invention comprises, the following group of diseases or disorders: delirium (F05), dementia (such as Alzheimer Disease (F00), vascular dementia (F01), dementia due to other general medical conditions (HIV disease (F02.4), head trauma (F06.8), Parkinson Disease (F02.3), Huntington Disease (F02.2), Pick Disease (F02.0), Creutzfeldt-Jacob Disease (F02.1) and other (F02.8)), substance-induced persisting dementia (F1x.6)), amnesic disorders due to a general medical condition (F06.8) or a substance-induced persisting amnesic disorder (F1x.6), mild cognitive impairment disorder (F06.7) and other cognitive disorders (F04). The above list of diseases is provided by way of example and is not intended to limit the invention.

For instance, Alzheimer Disease is a degenerative brain disease of unknown cause that is the most common form of dementia. Alzheimer Disease usually starts in late middle age or in old age as a memory loss for recent events spreading to memories for more distant events and progresses over the course of five to ten years to a profound intellectual decline characterized by dementia and personal helplessness. The disease is marked histologically by the degeneration of brain neurons especially in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid. Because dopamine receptor D4 (DRD4) antagonism can inhibit the behavioral disturbances

- merely aggression and confusion - caused by the degeneration of dopamine D2 receptors (*Esiri, M.M., The basis for behavioural disturbances in dementia, J. Neurol. Neurosurg. Psychiatry, 1996; 61(2):127-130.2*) accompanied with Alzheimer disease and 5-HT2A antagonism has an important boosting effect towards the effect of cholinesterase inhibitors such as used in the treatment by facilitating the affected dopamine release in the mesocortical dopamine pathways, a high selective D4/5-HT2A-antagonist would be a more preferable compound to combine with a cholinesterase inhibitor since this avoids the counteracting effect of the in the art used SDAs on the cognitive functioning by its dopamine receptor D2-antagonism.
- 10 These diseases and their diagnoses are very clearly defined in the "*International Statistical Classification of Diseases and Related Health Problems, 1989 Revision, Geneva, World Health Organization, 1992 (ICD-10)*". This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of neurodegenerative disorders and is commonly used in the field of neurology. According to
- 15 the ICD-10 classification, the cognitive disorders are classified under several classes of disorders, i.e. dispersed under categories F00 to F19 (see above: respective classification between parentheses). Following the DSM classification, however, they are grouped in one class of diseases or disorders.
- The terms "treatment", "treating", and the like, as used herein include amelioration or elimination of a developed mental disease or condition once it has been established or alleviation of the characteristic symptoms of such disease or condition. As used herein these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated
- 20 therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound or composition of the invention to a patient that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence or relapse-prevention of a disease or condition or of symptoms associated therewith, for instance after a period of
- 25 improvement. It should be clear that mental conditions may be responsible for physical complaints. In this respect, the term "treating" also includes prevention of a physical disease or condition or amelioration or elimination of the developed physical disease or condition once it has been established or alleviation of the characteristic symptoms of such conditions.
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As used herein, the term "medicament" also encompasses the terms "drug", "therapeutic", "potion" or other terms which are used in the field of medicine to indicate a preparation with therapeutic or prophylactic effect.

5 The present inventors not only found that the selective 5-HT_{2A} and D₄ antagonists, inverse agonists or partial agonists have an effect in augmenting the therapeutic effect or in providing a faster onset of the therapeutic effect of a diversity of other pharmaceutical compounds, i.e. also named "second compounds" in the present invention, in the treatment of specific diseases or disorders. A few examples of other pharmaceutical compounds whose effects are augmented or where the onset of the effect is fastened
10 upon simultaneous or fore-going treatment with a selective 5-HT_{2A} and D₄ antagonist, preferably pipamperon in a low dose, are nor-epinephrine re-uptake inhibitors, neuroleptic agents, dopamine antagonists, or compounds used for treating or alleviating musculoskeletal diseases or disorders. A further list of other pharmaceutical compounds or second compounds useful according to the invention is provided in Table 5. It should
15 be clear, given the general applicable character of the invention, that this list of other pharmaceutical compounds is very brief and that the invention should not be restricted to the ones exemplified herein. It should be clear that in the present invention, pipamperon is never to be seen as a "second compound".

According to the invention, it thus has been found that the compounds having a selective
20 5-HT_{2A} and D₄ antagonist, inverse agonist or partial agonist activity as described above are useful for augmenting the therapeutic effect of a second compound on a disease.

According to another embodiment of the invention, it has also been found that the compounds having a selective 5-HT_{2A} and D₄ antagonist, inverse agonist or partial agonist activity as described above are useful for providing a faster onset of the
25 therapeutic effect of a second compound on a disease.

From the above it should be clear that the selective 5-HT_{2A} and D₄ antagonist, inverse agonist or partial agonist is also named 'the first compound' in the embodiments of the invention.

According to the invention, when the 5-HT_{2A} and D₄ antagonist, inverse agonist or partial
30 agonist activity reside in separate compounds, the term "composition" may be used. Compositions of the invention comprise a first element having (i) a selective affinity for the D₄ receptor with a pK_i value equal to or higher than 8 towards the D₄ receptor and less than 8 towards other dopamine receptors, and a second element having (ii) a selective

affinity for the 5-HT_{2A} receptor with a pK_i value equal to or higher than 8 towards the 5-HT_{2A} receptor and less than 8 towards other 5-HT receptors.

The expression "the 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist" is used herein to indicate a single compound having both activities or to indicate the composition
5 comprising the activities in separate elements.

It should be clear that when, in the present invention, a composition of separate elements is used instead of a single compound, this composition of separate elements may be used in combination with another, i.e. a second, compound to augment the therapeutic effect of the other, i.e. the second, compound on the same or another disease.

10 When the 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements and the second compound are administered simultaneously, the compounds or active ingredients may be present in a single pharmaceutical composition or formulation. Alternatively the compounds or active ingredients are administered in separate pharmaceutical compositions or formulations for simultaneous or
15 separate use. The invention thus also relates to pharmaceutical compositions comprising pipamperon and a second compound of the invention and to the uses of these pharmaceutical compositions.

When the 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements of the invention are administered prior to the second compound
20 as defined, the 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements is administered at least during 1 day prior to said second compound. Preferably, the 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days prior to the administration of the second
25 compound. Preferably, the 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 2, 3, 4 or 5 weeks prior to the administration of the second compound, or even for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months prior to the administration of the second compound.

30 According to a preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT_{2A} and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of citalopram or for providing a faster onset of the therapeutic effect of citalopram.

Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalanarbonitrile hydro-bromide.

5 According to an embodiment, a daily dose of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

10 According to another preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT_{2A} and D₄ antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of fluvoxamine or for providing a faster onset of the therapeutic effect of fluvoxamine.

15 Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

20 According to an embodiment, a daily dose of active ingredient of fluvoxamine maleate ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered.

25 According to a preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT_{2A} and D₄ antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of selegiline or for providing a faster onset of the therapeutic effect of selegiline.

Selegiline or L-deprenyl or phenylisopropyl methyl propynyl amine is a monoamine oxidase B inhibitor (MAO-B inhibitor) and is the conventional name given for the compound of the formula (R)-(-)-N, α -dimethyl-N-(2-propynyl) phenethylamine - HCl.

30 According to an embodiment, a daily dose of active ingredient of MAO-B inhibitor, preferably selegiline, ranges between 5 and 60 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 40 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

Most of the second compounds herein described are known in the art and may be used in doses according to the supplier's or physician's prescription, or may be used according to specific embodiments described herein.

Also encompassed by the invention are pro-drugs to these second compounds or active metabolites of these compounds. For instance, for risperidone it is known that, among other products, bio transformation in the liver produces 9-hydroxyrisperidone, which is of the same pharmacological activity and intensity as parent risperidone. Therefore, also 9-hydroxyrisperidone, naturally produced or chemically synthesized may be used in the methods and uses according to the invention.

10 The term "active metabolite" as used herein relates to a therapeutically active compound produced by the metabolism of a parent drug. Drugs administered to treat diseases are usually transformed (metabolized) within the body into a variety of related chemical forms (metabolites), some of which may have therapeutic activity (an active metabolite).

15 The present invention also encompasses the use of these second compounds, administered in the form of a pharmaceutically acceptable salt in admixture with a suitable pharmaceutically acceptable excipient.

To prepare the pharmaceutical compositions, comprising the compounds or the combination of the first and second compound described herein, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for administration orally, nasal, rectally, percutaneously, transdermally, by parenteral, intramuscular, intravascular injection or intrathecal administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included.

The pharmaceutical compounds for treatment are intended for parenteral, topical, oral or local administration and generally comprise a pharmaceutically acceptable carrier and an amount of the active ingredient sufficient to reverse or prevent the bad effects of mental disorders. The carrier may be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration.

Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

The pharmaceutically acceptable excipients described herein, for example, vehicles, adjuvants, carriers or diluents, are well-known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one that is chemically inert to the active compounds and one that has no detrimental side effects or toxicity under the conditions of use.

The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration are merely exemplary and are in no way limiting. Overall, the requirements for effective pharmaceutical carriers for parenteral compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250, (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986). Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are suitable in the context of the present invention for application to skin.

Formulations suitable for oral administration require extra considerations considering the nature of the compounds and the possible breakdown thereof if such compounds are administered orally without protecting them from the digestive secretions of the gastrointestinal tract. Such a formulation can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable

surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, 5 microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose 10 and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. For 15 aerosol administration, the compounds are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of compounds are 0.01%-20% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, 20 palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the compounds, preferably 0.25-5%. The balance of the compounds is ordinarily propellant. A carrier can also be included as desired, e.g., lecithin for intranasal delivery. These aerosol 25 formulations can be placed into acceptable pressurized propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations may be used to spray mucosa.

30 It will be understood that, apart from daily doses, the compounds can be administered by other schedules. For instance, the present invention also contemplates depot injection, in which a long acting form of the active compound is injected into the body, such as the muscles. From there the active compound slowly enters the rest of the body, so one injection can last from 1 to 4 weeks or even multiple months. Other form of dosage administrations relate to "once-a-week" pills, in which the ingredient is slowly released

over a period of a week, and slow-release patches, e.g. a CDS (Continuous Delivery System), or Once-a-Day Transdermal Patches.

According to a further embodiment, the invention also relates to a method for preparing a compound or composition having a selective D4 and 5-HT_{2A} antagonist, reverse agonist
5 or partial agonist. The invention also relates to the compounds prepared by the claimed method, with the proviso that said compound is not an already known compound, such as pipamperon.

It should be clear that the compounds and compositions described herein are useful for treating any patient in need thereof. As used herein the term "patient" is not restricted to
10 humans but also to other mammals, for instance, domestic animals which may also suffer from any form of a mental disease or disorder described herein.

The second compounds of the invention can be further grouped according to their pharmacological profile, which is summarized in Table 6.

The present invention is now described in more detail by the following embodiments. The
15 compounds belonging to different pharmacological profiles can be further grouped according to their action on the same pathway or system as follows.

1: combination therapy with a 5-HT (serotonin) reuptake enhancer

The mental disorders which can be treated using compounds having a high selective
20 affinity for the 5-HT_{2A} and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT (serotonin) reuptake enhancer, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
25 disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically
30 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep

disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
5 from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
15 from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient

20

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT (serotonin) reuptake enhancer compound is tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, tianeptine is to be administered in a daily dose ranging between 25 and 50 mg
25 of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT (serotonin) reuptake enhancer, preferably tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
30 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders,
35 adjustment disorders, impulse control disorders, substance related disorder, personality

disorder, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

5 A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT (serotonin) reuptake enhancer is tianeptine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

10 2: combination therapy with a 5-HT₁ autoreceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a 5-HT₁ autoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, 15 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating 25 disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said 30 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT₁ autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT₁ autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 35 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
5 from or prior to the administration of a 5-HT₁ autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT₁ autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT₁ autoreceptor agonist compound is sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT₁ autoreceptor agonist, preferably sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of
20 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorder, antisocial behaviour, bereavement, occupational problem, problems related to
25 abuse or neglect and pain disorders.

3: combination therapy with a 5-HT_{1A} (serotonin 1A receptor) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
30 with a 5-HT_{1A} (serotonin 1A receptor) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-
35 related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{1A} (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT_{1A} (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{1A} (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT_{1A} (serotonin 1A receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT_{1A} (serotonin 1A receptor) agonist compound is chosen from the group consisting of MN-305, zalospirone, xaliproden, VPI-013 (also known as OPC-14523), tandospirone, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said 5-HT_{1A} (serotonin 1A receptor) agonist is xaliproden and is to be administered in a daily dose ranging between

1 and 2 mg of the active ingredient. Even more preferably, said 5-HT_{1A} (serotonin 1A receptor) agonist is bupropion (controlled release formulation) and is to be administered in a daily dose ranging between 150 and 450 mg of the active ingredient. Even more preferably, said 5-HT_{1A} (serotonin 1A receptor) agonist is gepirone and is to be administered in a daily dose, ranging between 20 and 80 mg of the active ingredient per day.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT_{1A} (serotonin 1A receptor) agonist, preferably chosen from the group consisting of MN-305, zalospirone, xaliproden, VPI-013 (also known as OPC-14523), tandospirone, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, more preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT_{1A} (serotonin 1A receptor) agonist is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT_{1A} (serotonin 1A receptor) agonist is bupropion (controlled release formulation), preferably provided in a unitary dose of between 150 and 450 mg of the active ingredient.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT_{1A} (serotonin 1A receptor) agonist is gepirone, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.

5

4: combination therapy with a 5-HT_{1A} (serotonin 1A receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a 5-HT_{1A} (serotonin 1A receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{1A} antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT_{1A} antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT_{1A} antagonist compound is chosen from the group consisting of robalzotan tartrate hydrate and NAD299 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

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The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT_{1A} antagonist, preferably chosen from the group consisting of robalzotan tartrate hydrate and NAD299, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous,
5 separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control
10 disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

5: combination therapy with a 5-HT_{1B} (serotonin 1B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective
15 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a 5-HT_{1B} (serotonin 1B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders,
20 adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically
25 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders,
30 adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{1B} antagonist compound to augment the therapeutic effect or to
35 provide a faster onset of the therapeutic effect of said 5-HT_{1B} antagonist compound,

further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT1B antagonist compound is chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1B antagonist, preferably chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

6: combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating

disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{2B} antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT_{2B} antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{2B} antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT_{2B} antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT_{2B} antagonist compound is agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT_{2B} antagonist, preferably agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour,

bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- 5 A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2B antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

7: combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound

- 10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 15
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 25
- 30
- 35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT_{2C} antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT_{2C} antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT_{2C} antagonist compound is chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT_{2C} antagonist, preferably chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT_{2C} antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

8: combination therapy with a 5-HT₃ (serotonin 3 receptor) antagonist compound
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a 5-HT₃ (serotonin 3 receptor) antagonist compound, are substance-related disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,
5 separate from or prior to the administration of a 5-HT₃ antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT₃ antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10 According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT₃ antagonist compound is ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, ondansetron is to be administered in a daily dose ranging between 8 and 32 mg of the active ingredient.

15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT₃ antagonist, preferably ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation
20 of substance-related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT₃ antagonist is ondansetron, preferably provided in a unitary dose
25 of between 8 and 32 mg of the active ingredient.

9: combination therapy with a 5-HT₆ (serotonin 6 receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
30 with a 5-HT₆ (serotonin 6 receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic
35 disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, 5 vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive 10 impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT₆ antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT₆ antagonist compound, further characterized in that pipamperon is to be administered to a 15 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT₆ antagonist compound is chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a 20 pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT₆ antagonist, preferably chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically 25 acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia 30 due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

10: combination therapy with an acetylcholinesterase inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an acetylcholinesterase inhibitor compound, are chosen from the group of diseases
5 or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive
10 impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and
15 disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive
20 impairment disorder, other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an acetylcholinesterase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said acetylcholinesterase inhibitor compound, further characterized in that pipamperon is to be
25 administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said acetylcholinesterase inhibitor compound is chosen from the group consisting
30 of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donepezil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, rivastigmine tartrate is to be administered in a daily dose ranging between 3 and 12 mg of
35 the active ingredient. Preferably, phenserine tartrate is to be administered in a daily dose ranging between 20 and 30 mg of the active ingredient. Preferably, galantamine

(extended release formulation) is to be administered in a daily dose ranging between 8 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an acetylcholinesterase inhibitor, preferably chosen from the group consisting of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donepezil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is rivastigmine tartrate, preferably provided in a unitary dose of between 3 and 12 mg of the active ingredient.

The invention further relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is phenserine tartrate, preferably provided in a unitary dose of between 20 and 30 mg of the active ingredient.

In addition, the invention relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is galantamine (preferably extended release formulation), preferably provided in a unitary dose of between 8 and 24 mg of the active ingredient.

11: combination therapy with an adenosine A2a receptor antagonist compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an adenosine A_{2a} receptor antagonist compound, is Parkinson disease.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
10 from or prior to the administration of an adenosine A_{2a} receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adenosine A_{2a} receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the use as described above, wherein said adenosine A_{2a} receptor antagonist compound is KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, KW-6002 is to be administered in a daily dose ranging between 40 and 80 mg of the
20 active ingredient

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adenosine A_{2a} receptor antagonist, preferably KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
25 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient
30 and wherein said acetylcholinesterase inhibitor is KW-6002, preferably provided in a unitary dose of between 40 and 80 mg of the active ingredient.

12: combination therapy with an adrenergic transmitter releaser

The mental disorders which can be treated using compounds having a high selective
35 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an adrenergic transmitter releaser, are chosen from the group of diseases or

disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said adrenergic transmitter releaser compound is pipoxazob or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, pipoxazole is to be administered in a daily dose ranging between 30 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adrenergic transmitter releaser, preferably pipoxazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
5 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment
10 disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient
15 and wherein said adrenergic transmitter releaser is pipoxazole, preferably provided in a unitary dose of between 30 and 60 mg of the active ingredient

13: combination therapy with an alpha 1 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective
20 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an alpha 1 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
25 disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
30 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders,
35 bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said alpha 1 adrenoreceptor antagonist compound is chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 1 adrenoreceptor antagonist, preferably chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

14: combination therapy with an alpha 2 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an alpha 2 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said
5 alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described
10 above, wherein said alpha 2 adrenoreceptor antagonist compound is chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, idazoxan is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 2 adrenoreceptor antagonist, preferably chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof,
20 or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious
25 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

30 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said alpha 2 adrenoreceptor antagonist is Idazoxan, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

15: combination therapy with an AMPA receptor mediator compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor
- 5 mediator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-induced
- 10 disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to
- 15 Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders
- 25 (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or
- 30 neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging
- 35 between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
5 from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced
15 persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized
20 in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15
25 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said AMPA receptor mediator compound is chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and
30 ampakine CX-516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
35 and (b) an AMPA receptor mediator, preferably chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-

516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is

5 chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality

10 disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,

15 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

16: combination therapy with an amphetamine compound

20 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an amphetamine compound, are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically

25 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amphetamine compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said

30 amphetamine compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said amphetamine compound is methylphenidate (preferably administered by a

35 transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amphetamine, preferably methylphenidate (preferably administered by a transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention deficit disorders.

17: combination therapy with an amyloid aggregation-inhibitor compound

10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an amyloid aggregation-inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia
15 due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
25 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
30 simultaneously with, separate from or prior to the administration of an amyloid aggregation-inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amyloid aggregation-inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said amyloid aggregation-inhibitor compound is chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, Alzhemed is to be administered in a daily dose of between 200 and 300 mg of the active ingredient

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amyloid aggregation-inhibitor, preferably chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said amyloid aggregation-inhibitor is Alzhemed, preferably provided in a unitary dose of between 200 and 300 mg of the active ingredient.

18: combination therapy with an androgen receptor modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an androgen receptor modulator compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an androgen receptor modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said androgen receptor modulator compound, further characterized in

that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said androgen receptor modulator compound is LGD2226 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an androgen receptor modulator, preferably LGD2226 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sexual and gender identity disorders.

19: combination therapy with an beta 3 adrenoreceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an beta 3 adrenoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound,

further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said beta 3 adrenoreceptor agonist compound is SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a beta 3 adrenoreceptor agonist, preferably SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

20: combination therapy with a calcium channel modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a calcium channel modulator compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick

Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
10 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
15 simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
25 from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 30 According to a preferred embodiment, the invention relates to the uses as described above, wherein said calcium channel modulator compound is chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a calcium channel modulator, preferably chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous,
5 separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to
10 Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

21: combination therapy with a cannaboid receptor 1 (CB1) antagonist

15 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a cannaboid receptor 1 (CB1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative
20 disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

25

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, psychotic
30 disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem
35 and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a cannabinoid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabinoid receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
5 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabinoid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabinoid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
15 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said
20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabinoid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabinoid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
25 ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said cannabinoid receptor antagonist compound is SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
30

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cannabinoid receptor antagonist, preferably SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying
35 emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic

disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, 5 malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

22: combination therapy with a cathepsin K inhibitor compound

The mental disorders which can be treated using compounds having a high selective 10 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a cathepsin K inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 15 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cathepsin K inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cathepsin K inhibitor compound, further characterized in that pipamperon is to be administered to a 20 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said cathepsin K inhibitor compound is 462795 or a pro-drug or an active 25 metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cathepsin K inhibitor, preferably 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation 30 of pain disorders.

23: combination therapy with a choline uptake enhancer compound

The mental disorders which can be treated using compounds having a high selective 35 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a choline uptake enhancer compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia,

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a choline uptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said choline uptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said choline uptake enhancer compound is MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, MKC-231 is to be administered in a daily dose of between 20 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a choline uptake enhancer, preferably MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein
5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient
and wherein said choline uptake enhancer is MKC-231, preferably provided in a unitary
dose of between 20 and 160 mg of the active ingredient.

24: combination therapy with a COX-2 inhibitor compound

10 The mental disorders which can be treated using compounds having a high selective
affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
with a COX-2 inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically
15 acceptable salt thereof for the preparation of a medicament for treating the underlying
emotion dysregulation of pain disorders, characterized in that pipamperon or said
pharmaceutically acceptable salt thereof is administered simultaneously with, separate
from or prior to the administration of a COX-2 inhibitor compound to augment the
therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-2
20 inhibitor compound, further characterized in that pipamperon is to be administered to a
patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above,
wherein said COX-2 inhibitor compound is chosen from the group consisting of
25 valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably
parecoxib, etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a
pharmaceutically acceptable salt thereof. Preferably, parecoxib is to be administered in a
daily dose of between 20 and 80 mg of the active ingredient. Preferably, etoricoxib is to be
administered in a daily dose of between 20 and 120 mg of the active ingredient.
30 Preferably, COX 189 is to be administered in a daily dose of between 100 and 800 mg of
the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
and (b) a COX-2 inhibitor, preferably chosen from the group consisting of valdecoxib,
35 rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib,
etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a

pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

- 5 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is parecoxib, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.
- 10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is etoricoxib, preferably provided in a unitary dose of between 20 and 120 mg of the active ingredient.
- 15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is COX 189, preferably provided in a unitary dose of between 100 and 800 mg of the active ingredient.
- 20 25: combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound, are pain disorders.
- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-inhibiting nitric oxide donator (CINOD)
- 30 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-inhibiting nitric oxide donator (CINOD) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 35 According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-inhibiting nitric oxide donator (CINOD) compound is chosen from the

group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, AZD3582 is to be administered in a daily dose ranging between 93.75 and 750 mg of the active ingredient

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-inhibiting nitric oxide donator (CINOD), preferably chosen from the group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain
10 disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-inhibiting nitric oxide donator (CINOD) is AZD3582, preferably
15 provided in a unitary dose of between 93.75 and 750 mg of the active ingredient.

26: combination therapy with a CRF1 (corticotropin-releasing factor receptor 1) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
20 with a CRF1 (Corticotropin-Releasing Factor receptor 1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders,
25 personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
30 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders,
35 personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt

thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said CRF1 antagonist compound is chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, R121919 is to be administered in a daily dose of between 5 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a CRF1 antagonist, preferably chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said CRF1 antagonist is R121919, preferably provided in a unitary dose of between 5 and 80 mg of the active ingredient.

5

27: combination therapy with a D1 (dopamine 1) receptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a D1 (dopamine 1) receptor agonist, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said D1 receptor agonist compound is DAS-431 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D1 receptor agonist, preferably DAS-431 or a pro-drug or an active metabolite

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thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

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28: combination therapy with D2 (dopamine 2) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with D2 (dopamine 2) receptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said

pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a
5 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said
10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said D2 receptor antagonist compound is chosen from the group consisting of bifeprunox and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of bifeprunox and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for
25 simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive
30 behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

29: combination therapy with D3 (dopamine 3) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with D₃ (dopamine 3) receptor antagonist, are chosen from the group of diseases or disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D₃ receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D₃ receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D₃ receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D₃ receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said
5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
15 from or prior to the administration of a D3 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20 According to a preferred embodiment, the invention relates to the uses as described above, wherein said D3 receptor antagonist compound is chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D3 receptor antagonist, preferably chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous,
30 separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions,
35 malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease.

30: combination therapy with a DA (dopamine) uptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
5 with a DA (dopamine) uptake inhibitor, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
10 emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered
15 to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said
20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25 According to a preferred embodiment, the invention relates to the uses as described above, wherein said DA uptake inhibitor compound is chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

30 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D₂ receptor antagonist, preferably chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous,
35 separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

31: combination therapy with an dopamine (receptor) agonist

- 5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an dopamine (receptor) agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be
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administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said dopamine (receptor) agonist compound is chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide, cabergoline, lisuride, preferably sumanirole, rotigotine (preferably a Once-a-Day Transdermal Patch), pergolide or ropinirole HCL (preferably controlled-release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, sumanirole is to be administered in a daily dose of between 4 and 16 mg of the active ingredient. Preferably, rotigotine (Once-a-Day Transdermal Patch) is to be administered in a daily dose of between 4.5 and 13.5 mg of the active ingredient. Preferably, ropinirole HCL (controlled-release formulation) is to be administered in a daily dose of between 0.75 and 24 mg of the active ingredient. Preferably, pergolide is to be administered in a daily dose of between 0.5 and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a dopamine (receptor) agonist, preferably chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide, cabergoline, lisuride and pergolide, more preferably sumanirole, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation) or pergolide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a

combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
5 factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is sumanirole, preferably provided in a unitary dose of between 4 and 16 mg of the active ingredient.

15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is rotigotine (Once-a-Day Transdermal Patch), preferably provided in a unitary dose of between 4.5 and 13.5 mg of the active ingredient.

20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is ropinirole HCL (controlled-release formulation), preferably provided in a unitary dose of between 0.75 and 24 mg of the active ingredient

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is pergolide, preferably provided in a unitary dose of between 0.5 and 10 mg of the active ingredient

30 32: combination therapy with a compound activating ERK (extracellular signal-related kinase)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
35 with a compound that activates ERK (extracellular signal-related kinase), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced

persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound that activates ERK (extracellular signal-related kinase) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound that activates ERK (extracellular signal-related kinase), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, CPI-1189 is to be administered in a daily dose of between 50 and 100 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound that activates ERK (extracellular signal-related kinase), preferably CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease,

dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189, preferably provided in a unitary dose of between 50 and 100 mg of the active ingredient.

33: combination therapy with a GABA (gamma-aminobutyric acid) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a GABA (gamma-aminobutyric acid) agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA agonist compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above,
5 wherein said GABA agonist compound is nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA agonist, preferably nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for
10 simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to
15 Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

20 34: combination therapy with a GABA-A agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) agonist compound, are sleep disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sleep disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
30 from or prior to the administration of a GABA-A agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35 According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-A agonist compound is gaboxadol or a pro-drug or an active

metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, gaboxadol is to be administered in a daily dose of between 5 and 20 mg of the active ingredient.

5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an GABA-A agonist, preferably gaboxadol or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sleep disorders.

10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A agonist is Gaboxadol, preferably provided in a unitary dose of between 5 and 20 mg of the active ingredient.

15 35: combination therapy with a GABA-A modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) modulator compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, 20 premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, 30 adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-A modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic 35 effect of said GABA-A modulator compound, further characterized in that pipamperon is to

be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-A modulator compound is chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, NGD 96-3, indiplon, eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), pagoclone, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, zolpidem MR sustained-release version is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, zaleplon extended-release is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient. Preferably, pagoclone is to be administered in a daily dose ranging between 7.5 and 60 mg of the active ingredient. Preferably, indiplon is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, eszopiclone is to be administered in a daily dose of between 2 and 3 mg of the active ingredient. Preferably, ocinaplon is to be administered in a daily dose of between 10 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-A modulator, preferably chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, indiplon, eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), pagoclone, NGD 96-3, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zolpidem MR sustained-release version, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zaleplon extended-release, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is Pagodone, preferably provided in a unitary dose of between 7.5 and 60 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is indiplon, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is eszopiclone, preferably provided in a unitary dose of between 2 and 3 mg of the active ingredient.

25

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is ocinaplon, preferably provided in a unitary dose of between 10 and 60 mg of the active ingredient.

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36: combination therapy with a GABA-B antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a GABA-B (gamma-aminobutyric acid receptor B) antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious

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disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
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- 15
- 20 According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-B antagonist compound is AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-B antagonist, preferably AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.
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- 30

37: combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound, is Parkinson disease.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
10 from or prior to the administration of a Glial-cell Line Derived Neurotrophic Factor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said Glial-cell Line Derived Neurotrophic Factor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the use as described above, wherein said Glial-cell Line Derived Neurotrophic Factor compound is GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, GDNF is to be administered in a daily dose ranging between 3.75 and 30 mg of the active
20 ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a Glial-cell Line Derived Neurotrophic Factor, preferably GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
25 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient
30 and wherein said Glial-cell Line Derived Neurotrophic Factor is GDNF, preferably provided in a unitary dose of between 3.75 and 30 mg of the active ingredient.

38: combination therapy with a glucocorticoid synthesis inhibitor compound

The mental disorders which can be treated using compounds having a high selective
35 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy

with a glucocorticoid synthesis inhibitor compound, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said glucocorticoid synthesis inhibitor compound is metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glucocorticoid synthesis inhibitor, preferably metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

39: combination therapy with a glutamate receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a glutamate receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 35 According to a preferred embodiment, the invention relates to the uses as described above, wherein said glutamate receptor antagonist compound is LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glutamate receptor antagonist, preferably LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
5 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement,
10 occupational problem, problems related to abuse or neglect and pain disorders.

40: combination therapy with an GPCR (G-protein-coupled receptor) modulator

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
15 with an GPCR (G-protein-coupled receptor) modulator, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality
20 disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
25 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders,
30 personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GPCR modulator compound, further characterized
35 in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GPCR modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

According to a preferred embodiment, the invention relates to the uses as described above, wherein said GPCR modulator compound is R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GPCR modulator, preferably R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders
20 consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain
25 disorders.

41: combination therapy with an GR (glucocorticoid receptor) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
30 with an GR (glucocorticoid receptor) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders,
35 bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said GR antagonist compound is chosen from the group consisting of ORG 34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, mifepristone is to be administered in a daily dose of between 600 and 1200 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GR antagonist, preferably chosen from the group consisting of ORG 34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GR antagonist is Mifepristone, preferably provided in a unitary dose of between 600 and 1200 mg of the active ingredient.

42: combination therapy with a histamine H3-receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a histamine H₃-receptor antagonist, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a histamine H₃-receptor antagonist compound to augment the therapeutic effect or to provide a faster

onset of the therapeutic effect of said histamine H3-receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 5 According to a preferred embodiment, the invention relates to the uses as described above, wherein said histamine H3-receptor antagonist compound is chosen from the group of compounds consisting of ABT-834 and ABT-239, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 10 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a histamine H3-receptor antagonist, preferably chosen from the group consisting of ABT-834 and ABT-239 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous,
- 15 mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-
- 20 induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

43: combination therapy with a hormonal substance

- The mental disorders which can be treated using compounds having a high selective
- 25 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a hormonal substance, are chosen from the group of diseases or disorders consisting of premenstrual syndrome and sexual and gender identity disorders.

- The present invention thus relates to the use of pipamperon or a pharmaceutically
- 30 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of premenstrual syndrome and sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the
- 35 administration of a hormonal substance to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said hormonal substance, further characterized in

that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said hormonal substance is chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said hormonal substance is synthetic conjugated estrogen A and is to be administered in a daily dose ranging between 0.075 and 0.6 mg of the active ingredient. More preferably, said hormonal substance is a drosiperone/ethinyl estradiol composition and is to be administered as a daily dose in tablets, preferably comprising 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a hormonal substance, preferably chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of premenstrual syndrome and sexual and gender identity disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said hormonal substance is synthetic conjugated estrogen A, preferably provided in a unitary dose of between 0.075 and 0.6 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said hormonal substance is a drosiperone/ethinyl estradiol composition, preferably provided in tablets comprising a unitary dose of 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

44: combination therapy with a compound which increases brain concentrations of 5-HT

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
5 with a compound which increases brain concentrations of 5-HT (serotonin), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-
10 related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
15 emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders,
20 personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound
25 which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
30 emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said
35 compound which increases brain concentrations of 5-HT (serotonin), further characterized

in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5 According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which increases brain concentrations of 5-HT (serotonin) is chosen from the group consisting of triptosine, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases brain concentrations of 5-HT (serotonin), preferably chosen from the group consisting of triptosine, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from
15 the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems
20 related to abuse or neglect and pain disorders.

45: combination therapy with a compound which increases insulin sensitivity

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
25 with a compound which increases insulin sensitivity, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic
30 disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
35 emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting

dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases insulin sensitivity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases insulin sensitivity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which increases insulin sensitivity is rosiglitazone maleate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases insulin sensitivity, preferably rosiglitazone maleate or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

46: combination therapy with a compound inhibiting the mixed lineage kinase family

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a compound which is an inhibitor of the mixed lineage kinase family is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is an inhibitor of the mixed lineage kinase family to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is an inhibitor of the mixed lineage kinase family, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which is an inhibitor of the mixed lineage kinase family is CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is an inhibitor of the mixed lineage kinase family, preferably CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

47: combination therapy with an interleukin-1 beta converting enzyme inhibitor compound
The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an interleukin-1 beta converting enzyme inhibitor compound, is a pain disorder.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an interleukin-1 beta converting enzyme inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said interleukin-1 beta converting enzyme inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said interleukin-1 beta converting enzyme inhibitor is pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an interleukin-1 beta converting enzyme inhibitor, preferably pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder,.

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48: combination therapy with a levodopa/decarboxylase inhibitor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a levodopa/decarboxylase inhibitor compound, is Parkinson Disease.

15

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
20 from or prior to the administration of a levodopa/decarboxylase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said levodopa/decarboxylase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

- According to a preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboxylase inhibitor compound is chosen from the group consisting of levodopa / carbidopa, levodopa / benserazide, etilevodopa / carbidopa or etilevodopa / benserazide, or a pro-drug or an active metabolite thereof, or a
30 pharmaceutically acceptable salt thereof. Preferably, levodopa / carbidopa is to be administered in a daily dose between 250 to 600 mg / 25 to 150 mg of the active ingredients. Preferably, levodopa / benserazide is to be administered in a daily dose between 100 to 600 mg / 25 to 150 mg of the active ingredients.

- 35 According to a further preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboxylase inhibitor compound is (eti)levodopa /

- carbiodopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, said levodopa/decarboxylase inhibitor
- 5 compound is levodopa/carbidopa and is to be administered in a dose ranging between 2000 mg/ 50 mg and 100 mg/ 10 mg of the active ingredients. Preferably said entacapone is to be administered in a dose ranging between 1000 mg/ 50 mg, more preferably between 500 mg/ 100 mg, and most preferably 200 mg of the active ingredients per day.
- 10 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboxylase inhibitor compound, preferably levodopa / carbidopa, levodopa / benserazide, etilevodopa / carbidopa or etilevodopa / benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the
- 15 underlying emotion dysregulation of Parkinson Disease. The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboxylase inhibitor compound, preferably is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug
- 20 or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.
- The invention also relates to a pharmaceutical composition as described above wherein
- 25 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboxylase inhibitor compound is levodopa / carbidopa, preferably provided in a unitary dose of between 250 to 600 mg and 25 to 150 mg of the active ingredients.
- 30 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboxylase inhibitor compound is levodopa / benserazide, preferably provided in a unitary dose of between 100 to 600 mg and 25 to 150 mg of the active ingredients.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboxylase inhibitor compound is levodopa / carbidopa or etilevodopa / carbidopa in combination with entacapone, of which the latter is preferably
5 provided in a unitary dose of between 500 mg and 100 mg of the active ingredient.

49: combination therapy with a lipid-DNA complex

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
10 with a lipid-DNA complex, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said
15 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of lipid-DNA complex to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said lipid-DNA complex, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20

According to a preferred embodiment, the invention relates to the use as described above, wherein said lipid-DNA complex is GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a lipid-DNA complex, preferably GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

30

50: combination therapy with a monoamine oxidase (MAO) reuptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase (MAO) reuptake inhibitor, are chosen from the group of
35 diseases or disorders consisting of substance related disorders and attention-deficit disorders (ADHD).

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of non-cognitive mental disease or disorder which are substance
5 related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that
10 pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
15 emotion dysregulation of attention-deficit disorders (ADHD), characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor
20 compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase (MAO) reuptake inhibitor compound is NS 2359
25 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase (MAO) reuptake inhibitor, preferably NS 2359 or a pro-drug
30 or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of substance related disorders and attention-deficit disorders (ADHD).

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51: combination therapy with a MAO-A and a MAO-B reuptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor, wherein said disorders are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound is SPD473 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably SPD473 or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention-deficit disorders.

52: combination therapy with a monoamine oxidase B (MAO-B) inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) inhibitor, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit

disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described
5 above, wherein said monoamine oxidase B (MAO-B) inhibitor compound is chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said monoamine oxidase B (MAO-B) inhibitor is selegiline and is to be administered in a daily dose ranging between 5 and 60 mg or possibly
10 between 5 and 10 mg of the active ingredient. In a further preferred embodiment, selegiline is to be administered in a transdermal application in a daily dose ranging between 5 and 60 mg of the active ingredient. In another preferred embodiment, selegiline is to be administered orally in a daily dose ranging between 5 and 10 mg of the active ingredient. More preferably, said monoamine oxidase B (MAO-B) inhibitor is rasagiline
15 (TVP-1012) and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) inhibitor, preferably chosen from the group
20 consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual
25 syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

30 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is selegiline, preferably provided in a unitary dose of between 5 and 10 mg or between 5 and 60 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012), preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

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53: combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor, is Parkinson Disease.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) reuptake inhibitor to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) reuptake inhibitor, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the use as described above wherein said monoamine oxidase B (MAO-B) reuptake inhibitor is safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

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54: combination therapy with a melanocortin-4 (MC4) receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a melanocortin-4 (MC4) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious

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disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanocortin-4 (MC4) receptor antagonist compound is MCL0129, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

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The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanocortin-4 (MC4) receptor antagonist compound, preferably MCL0129 or a

pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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55: combination therapy with a MCH receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a melanin concentrating hormone (MCH) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a
10 daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanin concentrating hormone (MCH) receptor antagonist compound is SNAP-7941 or a pro-drug or an active metabolite thereof, or a
15 pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanin concentrating hormone (MCH) receptor antagonist compound, preferably SNAP-7941 or a pro-drug or an active metabolite thereof, or a pharmaceutically
20 acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity
25 disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

56: combination therapy with a melatonin receptor (MT) agonist compound

30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a melatonin receptor (MT) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious
35 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality

disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melatonin receptor (MT) agonist compound is chosen from the group consisting of ramelteon and agomelatine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said melatonin receptor (MT) agonist compound is agomelatine and is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melatonin receptor (MT) agonist compound, preferably ramelteon or agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said melatonin receptor (MT) agonist compound is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

57: combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said metabotropic glutamate receptor (MgluR) agonist compound is PRE703 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a metabotropic glutamate receptor (MgluR) agonist, preferably PRE703 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

58: combination therapy with a compound mimicking the effect of nerve growth factor (NGF)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy

- with a compound which mimics the effect of nerve growth factor (NGF), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
- 15 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
- 20 simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
- 25 ingredient.
- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said
- 30 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose
- 35 ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which mimics the effect of nerve growth factor (NGF) is xaliproden and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which mimics the effect of nerve growth factor (NGF), preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

59: combination therapy with a muscarinic receptor partial agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a muscarinic receptor partial agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of

5 diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic

10 disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a muscarinic receptor partial agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said muscarinic receptor partial agonist compound, further

15 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said muscarinic receptor partial agonist compound is sevimeline or a pro-drug or

20 an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a muscarinic receptor partial agonist compound, preferably sevimeline or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a

25 combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick

30 Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

60: combination therapy with a selective nor-adrenaline re-uptake inhibitor (NARI) compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
5 with a selective nor-adrenaline re-uptake inhibitor (NARI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders,
15 adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI) compound to augment the therapeutic
20 effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI)
30 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35 According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is

chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200, 155U88, (S)-A 75200, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine and is to be administered in a daily dose ranging between
5 8 and 12 mg of the active ingredient. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride and is to be administered in a daily dose ranging between 40 and 100 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
10 and (b) a selective nor-adrenaline re-uptake inhibitor (NARI) compound, preferably chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200, 155U88, (S)-A 75200, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or
15 disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine, preferably provided in a unitary dose of between 8 and 12 mg of the active ingredient.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride, preferably provided in a unitary dose of between 40 and 100
30 mg of the active ingredient.

61: combination therapy with a NaSSA compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
35 with a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety

disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said noradrenergic/specific serotonergic antidepressant (NaSSA) compound is ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, preferably ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

62: combination therapy with a selective NDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment

the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline

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and dopamine re-uptake inhibitor (NDRI) compound is GW353162 and is to be administered in a daily dose ranging between 20 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, preferably GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162, preferably provided in a unitary dose of between 20 and 60 mg of the active ingredient.

63: combination therapy with a compound which is a neuroimmunophilin ligand

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a compound which is a neuroimmunophilin ligand, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a neuroimmunophilin ligand to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a neuroimmunophilin ligand, further characterized in that pipamperon

is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient

According to a preferred embodiment, the invention relates to the use as described above, wherein said a compound which is a neuroimmunophilin ligand is GPI 1485 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said a compound which is a neuroimmunophilin ligand is GPI 1485 and is to be administered in a daily dose ranging between 200 and 1000 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a neuroimmunophilin ligand, preferably GPI 1485 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said a compound which is a neuroimmunophilin ligand is GPI 1485, preferably provided in a unitary dose of between 200 and 1000 mg of the active ingredient.

64: combination therapy with a neuromodulator compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a neuromodulator compound, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neuromodulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neuromodulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neuromodulator compound is adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neuromodulator compound, preferably adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

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65: combination therapy with a neurotensin receptor antagonist compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a neurotensin receptor antagonist compound, are chosen from the group of diseases
- 15 or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering,
- 20 antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
- 25 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related
- 30 disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to
- 35 augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to

be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neurotensin receptor antagonist compound is SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurotensin receptor antagonist compound is SR 48692 and is to be administered in a daily dose ranging between 90 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurotensin receptor antagonist compound, preferably SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep

disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to
5 abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurotensin receptor antagonist compound is SR 48692, preferably
10 provided in a unitary dose of between 90 and 300 mg of the active ingredient.

66: combination therapy with nerve growth factor (NGF) gene therapy

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
15 with nerve growth factor (NGF) gene therapy, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general
20 medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
25 emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic
30 disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nerve
35 growth factor (NGF) gene therapy, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound useful in nerve growth factor (NGF) gene therapy, preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

It should be understood that "nerve growth factor gene therapy" is well known in the art, and the compounds, for instance nucleic acids used in nerve growth factor gene therapy are well described (see e.g. Tuszynski *et al.*, (2002) Journal of Molecular Neuroscience Volume 19, Issue 1-2, pps. 207-208).

67: combination therapy with a nicotinic acetylcholine receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a nicotinic acetylcholine receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse

control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said nicotinic acetylcholine receptor antagonist compound is SEP174559 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic acetylcholine receptor antagonist compound, preferably SEP174559 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the

underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

68: combination therapy with a nicotinic receptor agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a nicotinic receptor agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said nicotinic receptor agonist compound is ABT-089, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said

nicotinic receptor agonist compound is ABT-089 and is to be administered in a daily dose ranging between 4 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic receptor agonist compound, preferably ABT-089 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said nicotinic receptor agonist compound is ABT-089, preferably provided in a unitary dose of between 4 and 40 mg of the active ingredient.

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69: combination therapy with a neurokinin 2 receptor (NK2) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a neurokinin 2 receptor (NK2) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),

factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurokinin 2 receptor (NK2) antagonist compound is saredutant and is to be administered in a daily dose ranging between 25 and 200 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurokinin 2 receptor (NK2) antagonist compound, preferably saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders,

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bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein
5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient
and wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant,
preferably provided in a unitary dose of between 25 and 200 mg of the active ingredient.

70: combination therapy with a neurokinin 3 receptor (NK3) antagonist compound

10 The mental disorders which can be treated using compounds having a high selective
affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
with a neurokinin 3 receptor (NK3) antagonist compound, are chosen from the group of
diseases or disorders consisting of mood disorders, anxiety disorders, psychotic
disorders, somatoform disorders (excluding pain disorders), factitious disorders,
15 dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders,
pervasive development disorders, disruptive behaviour disorders, substance-related
disorders, personality disorders, psychological factors affecting medical conditions,
malingering, antisocial behaviour, bereavement, occupational problem, identity problem,
problems related to abuse or neglect, pain disorders and delirium.

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The present invention thus relates to the use of pipamperon or a pharmaceutically
acceptable salt thereof for the preparation of a medicament for treating the underlying
emotion dysregulation of a non-cognitive mental disease or disorder selected from the
group of diseases and disorders consisting of mood disorders, anxiety disorders,
25 psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders,
dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders,
pervasive development disorders, disruptive behaviour disorders, substance-related
disorders, personality disorders, psychological factors affecting medical conditions,
malingering, antisocial behaviour, bereavement, occupational problem, identity problem
30 and problems related to abuse or neglect, characterized in that pipamperon or said
pharmaceutically acceptable salt thereof is administered simultaneously with, separate
from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound
to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of
said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that
35 pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15
mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15
10 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium,
15 characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a
20 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable
25 salt thereof. More preferably, said neurokinin 3 receptor (NK3) antagonist compound is talnetant and is to be administered in a daily dose ranging between 1.5 and 12 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
30 and (b) a neurokinin 3 receptor (NK3) antagonist compound, preferably talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders,
35 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive

development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant, preferably provided in a unitary dose of between 1.5 and 12 mg of the active ingredient

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71: combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-

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aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is chosen from the group consisting of SEP174559, memantine, delucemine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said N-

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Methyl-D-aspartate (NMDA) antagonist compound is memantine and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an N-Methyl-D-aspartate (NMDA) antagonist compound, preferably chosen from the group consisting of SEP174559, memantine, delucemine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is memantine, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

72: combination therapy with a non-steroidal anti-inflammatory drug

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a non-steroidal anti-inflammatory drug, is a pain disorder or Alzheimer Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-

steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disease, such as Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said a non-steroidal anti-inflammatory drug is chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

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The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a non-steroidal anti-inflammatory drug, preferably chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder or Alzheimer Disease.

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73: combination therapy with an opioid receptor antagonist compound

- 30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an opioid receptor antagonist compound, are substance related disorders.

It will be appreciated that the terms "opoid" and "opioid" may be used interchangeably.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an opioid receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opioid receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the use as described above, wherein said opioid receptor antagonist compound is naltrexone, preferably as a depot formulation, more preferably in the form of microcapsules, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, said naltrexone is to be administered in the form of a depot, preferably a depot of microcapsules comprising a daily dose of between 192 and 384 mg.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an opioid receptor antagonist, preferably naltrexone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of substance related disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said opioid receptor antagonist compound is naltrexone, preferably provided in a unitary dose of between 192 and 384 mg of the active ingredient.

74: combination therapy with an opioid agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with an opioid agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an opioid agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opioid agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said opioid agonist compound is chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an opioid agonist compound, preferably chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

75: combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound, are chosen from the group of

5 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease,

10 substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive

15 disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the

20 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that

25 pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging

30 between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said

35 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound d

to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting
10 dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized
15 in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging
20 between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phosphodiesterase-4 (PDE4) inhibitor compound is chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active
25 metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a phosphodiesterase-4 (PDE4) inhibitor antagonist compound, preferably chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active
30 metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative
35 disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to

abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

76: combination therapy with a peptidic compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a peptidic compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic

effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic
10 effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,
20 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to
25 augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- According to a preferred embodiment, the invention relates to the uses as described
30 above, wherein said peptidic compound is chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said peptidic compound is secretin and is to be administered in a daily dose ranging between 0.2 and 0.4 mg/kg of the active ingredient. More preferably, said peptidic compound is INN 00835
35 and is to be administered in a daily dose ranging between 18 and 160 mg of the active ingredient.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a peptidic compound, preferably chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.
- 20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is secretin, preferably provided in a unitary dose of 0.2 and 0.4 mg/kg of the active ingredient.
- 25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is INN 00835, preferably provided in a unitary dose of 18 and 160 mg of the active ingredient.
- 30 77: combination therapy with a phospholipase A2 inhibitor compound
- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a phospholipase A₂ inhibitor compound which has caspase inhibitor activity, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual

and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders,
10 psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems
15 related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity,
20 further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
25 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase
30 inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
35 emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further
5 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phospholipase A2 inhibitor compound which has caspase inhibitor
10 activity is chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, preferably LAX-101c, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
15 and (b) a phospholipase A2 inhibitor compound which has caspase inhibitor activity, preferably chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, more preferably LAX-101c, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or
20 disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related
25 disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

78: combination therapy with a compound which is a prodrug of uridine

The mental disorders which can be treated using compounds having a high selective
30 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a compound which is a prodrug of uridine, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
35 disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a prodrug of uridine is RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a prodrug of uridine, preferably RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from

the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational
5 problem, problems related to abuse or neglect and pain disorders.

79: combination therapy with prostaglandin E1 compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
10 with prostaglandin E1 compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the
15 group of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a prostaglandin E1 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said prostaglandin E1 compound, further characterized in that pipamperon is to be
20 administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said prostaglandin E1 is alprostadil or a pro-drug or an active metabolite thereof,
25 or a pharmaceutically acceptable salt thereof. More preferably, said prostaglandin E1 compound is alprostadil, preferably in the form of cream or gel, preferably a topical gel, and is to be administered in a daily dose ranging between 50 and 300 microgram per application of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a prostaglandin E1 compound, preferably alprostadil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of
35 sexual and gender identity disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said prostaglandin E1 compound is alprostadiol, preferably provided in the form of a cream or gel, preferably a topical gel, wherein a unitary dose comprises between
5 50 and 300 microgram of the active ingredient per application.

80: combination therapy with a compound protecting dopaminergic and cholinergic neurons

The mental disorders which can be treated using compounds having a high selective
10 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a compound which protects dopaminergic and cholinergic neurons, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,
15 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
25 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
30 simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
35 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
5 from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which protects dopaminergic and cholinergic neurons is SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

15

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which protects dopaminergic and cholinergic neurons, preferably SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for
20 treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic
25 disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

81: combination therapy with a psycho stimulant

30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a psycho stimulant, are chosen from the group of diseases or disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
5 from or prior to the administration of a psycho stimulant to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said psycho stimulant, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10 According to a preferred embodiment, the invention relates to the uses as described above, wherein said psycho stimulant is chosen from the group consisting of SPD 503, r-modafinil and modafinil, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said psycho stimulant is SPE
15 503, more preferably said psycho stimulant is modafinil and is to be administered in a daily dose ranging between 200 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a psycho stimulant, preferably chosen from the group consisting of SPD 503, r-modafinil and modafinil, more preferably said SPC 503 or modafinil or a pro-drug or an
20 active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said psycho stimulant is modafinil, preferably provided in a unitary dose of between 200 and 600 mg of the active ingredient

30 82: combination therapy with a compound which is a Reversible Inhibitor of Mono-Amine oxydase A (RIMA)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy
35 with a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety

disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite

thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), preferably chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for
10 simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality
15 disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient
20 and wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

83: combination therapy with a compound which modulates SCT-11

- 25 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a compound which modulates SCT-11 (i.e. SCT-11 is a G protein-coupled receptor), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding
30 pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which modulates SCT-11 is SNEC-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which modulates SCT-11, preferably SNE-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders,

impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

84: combination therapy with a serotonin/dopamine antagonist compound (SDA)

5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a serotonin/dopamine antagonist compound (SDA), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders,
10 dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders,
20 psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem
25 and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to
30 be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
35 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said serotonin/dopamine antagonist compound is chosen from the group consisting of zotepine, ziprasidone, SM-13496, SL 91.0177, sertindole, S-18327, risperidone, quetiapine fumarate (preferably sustained release formulation), quetiapine fumarate (preferably granules), quetiapine, perospirone, paliperidone, olanzapine, ocaperidone, LU 31-131, iloperidone, clozapine, BSF-190555, blonanserin, bifeprunox, asenapine and aripiprazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said serotonin/dopamine antagonist compound is chosen from the group consisting of SL 91.0177, sertindole, perospirone, paliperidone, blonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said serotonin/dopamine antagonist compound is sertindole and is to be administered in a daily dose ranging between 12 and 24 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is paliperidone and is to be administered in a daily dose ranging between 3 and 15 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is asenapine and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a serotonin/dopamine antagonist compound, preferably chosen from the group

consisting of SL 91.0177, sertindole, perospirone, paliperidone, blonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is sertindole, preferably provided in a unitary dose of between 12 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is paliperidone, preferably provided in a unitary dose of between 3 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is asenapine, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

85: combination therapy with a selective SDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a selective serotonin and dopamine re-uptake inhibitor (SDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or

neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group

- of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and dopamine reuptake inhibitor (SDRI) compound is bazinaprine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and dopamine reuptake inhibitor (SDRI) compound, preferably bazinaprine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

86: combination therapy with a second messenger beta agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a second messenger beta agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

10

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35

According to a preferred embodiment, the invention relates to the uses as described above, wherein said second messenger beta agonist compound is chosen from the group consisting of SR 57227, rolipram and eplivanserin, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said second messenger beta agonist compound is rolipram and is to be administered in a daily dose ranging between 1.5 and 3 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a second messenger beta agonist compound, preferably chosen from the group consisting of SR 57227, rolipram and eplivanserin or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said second messenger beta agonist compound is rolipram, preferably provided in a unitary dose of between 1.5 and 3 mg of the active ingredient.

87: combination therapy with a secretin pancreatic hormone

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a secretin pancreatic hormone, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35

According to a preferred embodiment, the invention relates to the uses as described above, wherein said secretin pancreatic hormone is RG1068 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a secretin pancreatic hormone, preferably RG1068, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group
- 10 consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement,
- 15 occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

88: combination therapy with a sigma receptor agonist compound

- The mental disorders which can be treated using compounds having a high selective
- 20 affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a sigma receptor agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
- 25 disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- The present invention thus relates to the use of pipamperon or a pharmaceutically
- 30 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep
- 35 disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem and problems related to abuse

or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further
5 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
10 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further characterized in that pipamperon is to be administered
15 to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor agonist compound is VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or
20 an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor agonist compound, preferably VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or
25 an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative
30 disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

89: combination therapy with a sigma receptor antagonist compound

35 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy

- with a sigma receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect,, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor antagonist compound is chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said sigma receptor antagonist compound is EMD 68843 and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor antagonist compound, preferably chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sigma receptor antagonist compound is EMD 68843, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient

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90: combination therapy with a selective SNDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

- emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound is selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947; more preferably NS 2330 or DOV 216,303; or a pro-drug or an active metabolite thereof; or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, preferably selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947, more preferably NS 2330 or DOV 216,303, or a pro-drug or an

active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, 5 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, 10 dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder and other cognitive disorders.

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91: combination therapy with a selective SNRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, are 20 chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational 25 problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the 30 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related 35 to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the

administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose
5 ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a
15 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is selected from the group consisting of venlafaxine, tomoxetine, tandamine, talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine
20 and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is chosen from the group consisting of venlafaxine, tomoxetine, milnacipran, duloxetine and desvenlafaxine, or a pro-drug or an active
25 metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine and is to be administered in a daily dose ranging between 75 and 300 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine and is to be administered in a daily dose ranging
30 between 0.475 and 3.8 mg/kg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran and is to be administered in a daily dose ranging between 50 and 200 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is duloxetine and is to be administered in a daily dose ranging between 40 and
35 60 mg of the active ingredient.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, preferably selected from the group consisting of venlafaxine, tomoxetine, tandamine, talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine, preferably provided in a unitary dose of between 75 and 300 mg of the active ingredient.
- 20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine, preferably provided in a unitary dose of between 0.475 and 3.8 mg/kg of the active ingredient.
- 25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran, preferably provided in a unitary dose of between 50 and 200 mg of the active ingredient.
- 30 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI)
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compound is duloxetine, preferably provided in a unitary dose of between 40 and 60 mg of the active ingredient.

92: combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound

- 5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
- 10 factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
- 20 factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a
- 25 selective serotonin re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin re-uptake inhibitor (SSRI)
- 35 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin re-uptake inhibitor (SSRI) compound is selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA 21-004, Lu 35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is chosen from the group consisting of litoxetine, fluvoxamine (controlled release formulation), citalopram and escitalopram, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation) and is to be administered in a daily dose ranging between 100 and 300 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram and is to be administered in a daily dose ranging between 10 and 20 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram and is to be administered in a daily dose ranging between 10 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin re-uptake inhibitor (SSRI) compound, preferably selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA 21-004, Lu 35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, venlafaxine, milnacipran, duloxetine, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders,

personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- The invention also relates to a pharmaceutical composition as described above wherein
- 5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation), preferably provided in a unitary dose of between 100 and 300 mg of the active ingredient.
- 10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.
- 15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram, preferably provided in a unitary dose of between 10 and 40 mg of the active ingredient.
- 20 Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile-hydro-bromide. According to an embodiment, a daily doses of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of
- 25 active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.
- Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) re-uptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is
- 30 chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

According to an embodiment, a daily dose of active ingredient of fluvoxamine in a controlled release mode ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered in a

controlled release mode. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered by controlled release.

93: combination therapy with a substance P receptor (NK1) antagonist compound

- 5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a substance P receptor (NK1) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious
- 10 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
- 20 factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of
- 25 a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the
- 35 therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5 According to a preferred embodiment, the invention relates to the uses as described above, wherein said substance P receptor (NK1) antagonist compound is chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said substance P receptor (NK1) antagonist compound is aprepitant and is to be administered in a daily dose ranging
10 between 40 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a substance P receptor (NK1) antagonist compound, preferably chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-
15 122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome,
20 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said substance P receptor (NK1) antagonist compound is aprepitant, preferably provided in a unitary dose of between 40 and 160 mg of the active ingredient.

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94: combination therapy with a sulfonamide compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a sulfonamide compound, are chosen from the group of diseases or disorders
35 consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment

disorders, impulse control disorders, pervasive development disorders, disruptive
behaviour disorders, substance-related disorders, personality disorders, psychological
factors affecting medical conditions, malingering, antisocial behaviour, bereavement,
occupational problem, identity problem, problems related to abuse or neglect, pain
5 disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically
acceptable salt thereof for the preparation of a medicament for treating the underlying
emotion dysregulation of a non-cognitive mental disease or disorder selected from the
10 group of diseases and disorders consisting of mood disorders, psychotic disorders,
somatoform disorders (excluding pain disorders), factitious disorders, dissociative
disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive
development disorders, disruptive behaviour disorders, substance-related disorders,
personality disorders, psychological factors affecting medical conditions, malingering,
15 antisocial behaviour, bereavement, occupational problem, identity problem and problems
related to abuse or neglect, characterized in that pipamperon or said pharmaceutically
acceptable salt thereof is administered simultaneously with, separate from or prior to the
administration of a sulfonamide compound to augment the therapeutic effect or to provide
a faster onset of the therapeutic effect of said sulfonamide compound, further
20 characterized in that pipamperon is to be administered to a patient in a daily dose ranging
between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically
acceptable salt thereof for the preparation of a medicament for treating the underlying
25 emotion dysregulation of pain disorders, characterized in that pipamperon or said
pharmaceutically acceptable salt thereof is administered simultaneously with, separate
from or prior to the administration of a sulfonamide compound to augment the therapeutic
effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound,
further characterized in that pipamperon is to be administered to a patient in a daily dose
30 ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically
acceptable salt thereof for the preparation of a medicament for treating the underlying
emotion dysregulation of a cognitive mental disease or disorder which is delirium,
35 characterized in that pipamperon or said pharmaceutically acceptable salt thereof is
administered simultaneously with, separate from or prior to the administration of a

sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sulfonamide compound is zonisamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said sulfonamide compound is zonisamide and is to be administered in a daily dose ranging
10 between 100 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sulfonamide compound, preferably zonisamide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
15 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive
20 behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sulfonamide compound is zonisamide, preferably provided in a unitary dose of between 100 and 600 mg of the active ingredient.

30 95: combination therapy with a tachykinin antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a tachykinin antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual
35 syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
10 factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of
15 a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a tachykinin antagonist compound to augment the
25 therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- According to a preferred embodiment, the invention relates to the use as described above,
30 wherein said tachykinin antagonist compound is SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a tachykinin antagonist compound, preferably SR 48968 or a pro-drug or an active
35 metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

96: combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders,

- pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem and
- 5 problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic
- 10 effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient:
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of
- 20 R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging
- 25 between 5 and 15 mg of the active ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the
- 30 group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting
- 35 amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson

Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnesic disorders due to a general medical condition, substance-induced persisting amnesic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

5

97: combination therapy with a vasopressin 1B receptor (V1B) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a vasopressin 1B receptor (V1B) antagonist compound, are chosen from the group of

10 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and

15 pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the

20 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse

25 or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a

30 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said

35 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist

compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

According to a preferred embodiment, the invention relates to the uses as described above, wherein said vasopressin 1B receptor (V1B) antagonist compound is SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a vasopressin 1B receptor (V1B) antagonist compound, preferably SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

98: combination therapy with a voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

- emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 25 According to a preferred embodiment, the invention relates to the uses as described above, wherein said voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound is pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound is pregabalin, and is to be administered in a daily dose ranging between 50 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound, preferably pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound is pregabalin, preferably provided in a unitary dose of between 50 and 600 mg of the active ingredient.

99: combination therapy with a vomeropherin compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a vomeropherin compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of vomeropherin compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vomeropherin compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said vomeropherin compound is PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) vomeropherin compound, preferably PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of fluvoxamine controlled release, phenserine tartrate, atomoxetine hydrochloride, bupropion (controlled-release formulation), ropinirole HCL (controlled-release formulation), INN 00835, galantamine (extended release formulation), paliperidone, tomoxetine, aprepitant, rivastigmine tartrate, ORG 34517/34850, sunepitron, sumanirole, milnacipran, idazoxan, xaliproden, SR 58611, befloxatone, litoxetine, tianeptine, agomelatine, SPD 503, flesinoxan, bifeprunox, ramelteon, etilevodopa, rasagiline (TVP-1012) and desvenlafaxine.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of galantamine (extended release formulation), R121919, risperidone, paliperidone and R228060 (YKP-10A).

30 100: combination therapy with a dopamine releaser

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT_{2A} and D₄ receptor, for instance pipamperon, in a combination therapy with a dopamine releaser, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome,

somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
10 factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine releaser compound to augment the
15 therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
20 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine releaser compound, further characterized in that pipamperon is to be administered to a
25 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
30 from or prior to the administration of a dopamine releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- According to a preferred embodiment, the invention relates to the uses as described
35 above, wherein said dopamine (receptor) agonist compound is amantadine, or a pro-drug

or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, amantadine is to be administered in a daily dose of between 100 and 300 mg of the active ingredient.

5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a dopamine (receptor) agonist, preferably amantadine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, 10 premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is amantadine, preferably provided in a unitary dose of between 100 and 300 mg of the active ingredient.

20 From the above it will be apparent that the numbering of the grouping according to the action on the pathway or system corresponds to the numbering of the columns in Table 5 and the numbering of the pharmacological profile in Table 6.

25 The disclosure of all patents, publications (including published patent publications), and database accession numbers and depository accession numbers referenced in this specification are specifically incorporated herein by reference in their entirety to the same extent as if each such individual patent, publication, and database accession number, and depository accession number were specifically and individually indicated to be incorporated by reference.

30 The invention, now being generally described, will be more readily understood by reference to the following tables and examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention.

Short description of the Tables and Figures

Table 1: In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine₁ receptor.

5

Table 2: Set-up of a clinical trial comprising for treatment groups.

Table 3: Overview of a placebo, active and period controlled clinical trial in a fore-going pipamperon - citalopram treatment in Major Depressive Disorder.

10

Table 4: POC process for major depressive disorder.

Table 5: Summary of diseases and disorders relative to known psycho-tropics.

15 **Table 6:** Overview of Pharmacological grouping, indicating pharmacological profile numbering (column 2), pharmacological profile (column 3), main indication(s) (column 4), name of the compound (column 4), the dose range (column 5), and the company producing or selling said compound (column 6). Compounds indicated by hatching are preferred.

20

Figure 1: Add-on treatment with pipamperon after treatment with citalopram .

Figure 2: HDRS-17 change from baseline: combo treatment pipamperon as add-on - citalopram vs SNRI (duloxetine) in Major Depression.

25

Figure 3: Remission rates (HDRS-17 ≤ 7): combo treatment pipamperon as add-on - citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in Major Depression.

30 **Figure 4:** Fore-going treatment during 1-5 days with pipamperon followed with the combination treatment of pipamperon and citalopram.

Figure 5: HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (duloxetine) in Major Depression.

35

Figure 6: Remission rates (HDRS-17 ≤ 7): combo pipamperon - citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (venlafaxine) in Major Depression.

- 5 **Figure 7:** Fore-going treatment during 6-8 days with pipamperon followed with the combination treatment of pipamperon and citalopram.

- Figure 8:** HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 7 days with pipamperon vs SNRI (duloxetine) in Major
10 Depression.

Figure 9: Fore-going and add-on treatment with pipamperon in MDD.

- Figure 10:** HDRS-17 change from baseline: fore-going and add-on treatment with
15 pipamperon and citalopram in comparison with the SNRI duloxetine in Major Depression.

Figure 11: Remission rates (HDRS-17 ≤ 7): fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI venlafaxine in Major Depression.

- 20 **Figure 12:** Y-BOCS total score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

- Figure 13:** Y-BOCS obsession score: fore-going and add-on treatment with
25 pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

Figure 14: Y-BOCS compulsion score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.

- Figure 15:** CGI-severity score: fore-going and add-on treatment with pipamperon and
30 citalopram in comparison with the SSRI in panic disorder.

Table 1

	D1	D2	D3	D4	SHT _{1A}	SHT _{1B}	SHT _{1D}	SHT _{1E}	SHT _{1F}	SHT _{2A}	SHT _{2B}	SHT _{2C}	SHT _{6rat}	SHT _{7rat}	Alphal	Alphaz	Alphaz	Alphaz	Beta1	Beta2	H1
ORG5222	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	<6
Zotepine	0	<6	<6	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	<6
Fluparoxan	0	<6	<6	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Olanzapine	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	<6
Clozapine	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	<6
S16924	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	<6
S18327	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Amperozide	6-7	6-7	6-7	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
GGR218231	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Sertindole	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
MDL100,907	6-7	<6	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	6-7
Haloperidol	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Tiospirone	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	6-7
Raclopride	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Fluspirilene	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Ocaperidone	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Risperidone	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	7-8
S33084	6-7	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
L741626	6-7	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Seroquel	6-7	6-7	6-7	7-8	7-8	7-8	7-8	7-8	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	0	0
Yohimbine	0	6-7	<6	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	7-8
Ziprasidone	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	0	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	7-8
Pipamperon	0	6-7	6-7	7-8	7-8	7-8	7-8	7-8	<6	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	7-8	<6	<6	<6

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Table 2

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ACUTE PHASE**										EXTENSION PHASE***										FOLLOW-UP PHASE									
VISITS	V1 Screen minus D7	V2 Baseline D0	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19										
Day / Week / Month			D4	D7	D2	D3	D4	D5	D8	D10	D12	D16	D20	D24	D3	D10	D12	D17	D18	D19									
TREATMENT GROUP																													
Group PIP-Active / D7	A	B	B	C																									
Group PIP-Active / D4	A	B	C																										
Group PIP-Active / D0	A	C																											
Group PIP-Active / D0	A	D																											
Informed Consent																													
NECT																													
Vital Signs / Weight																													
LAB																													
ECG																													
Phys Exam																													
Alc/Drugs Screen																													
CGI-S****																													
Q-LES-Q*****																													
Treatment regimen:																													

Treatment regimen:

A: PLC + PLC

B: 2x(PLC+PIP(4mg))/d

C: 2x(CIT(10mg)+PIP(4mg))/d

D: 2x(CIT(10mg)+PLC)/d

*Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of:

**Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

***Entering Extension Phase: only remitters as defined by the DSM-IV criteria of efficacy

****CGI-S : Clinical Global Impressions-Improvement Scale

*****Q-LES-Q : Quality of Life, Enjoyment and Satisfaction Questionnaire

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Table 3

FOREGOING PIPAMPERON - CITALOPRAM TREATMENT IN MAJOR DEPRESSIVE DISORDER A PLACEBO, ACTIVE AND PERIODICALLY CONTROLLED																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
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ACUTE PHASE**					EXTENSION PHASE***															FOLLOW-UP PHASE																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
VISITS DAY/WEEK/MONTH	SCREEN minusc D7	W2 BASELINE D0	W3 D1	W4 D2	W5 D3	W6 D4	W7 D5	W8 D6	W9 D7	W10 D8	W11 D9	W12 D10	W13 D11	W14 D12	W15 D13	W16 D14	W17 D15	W18 D16	W19 D17	W20 D18	W21 D19	W22 D20	W23 D21	W24 D22	W25 D23	W26 D24	W27 D25	W28 D26	W29 D27	W30 D28	W31 D29	W32 D30	W33 D31	W34 D32	W35 D33	W36 D34	W37 D35	W38 D36	W39 D37	W40 D38	W41 D39	W42 D40	W43 D41	W44 D42	W45 D43	W46 D44	W47 D45	W48 D46	W49 D47	W50 D48	W51 D49	W52 D50	W53 D51	W54 D52	W55 D53	W56 D54	W57 D55	W58 D56	W59 D57	W60 D58	W61 D59	W62 D60	W63 D61	W64 D62	W65 D63	W66 D64	W67 D65	W68 D66	W69 D67	W70 D68	W71 D69	W72 D70	W73 D71	W74 D72	W75 D73	W76 D74	W77 D75	W78 D76	W79 D77	W80 D78	W81 D79	W82 D80	W83 D81	W84 D82	W85 D83	W86 D84	W87 D85	W88 D86	W89 D87	W90 D88	W91 D89	W92 D90	W93 D91	W94 D92	W95 D93	W96 D94	W97 D95	W98 D96	W99 D97	W100 D98	W101 D99	W102 D100	W103 D101	W104 D102	W105 D103	W106 D104	W107 D105	W108 D106	W109 D107	W110 D108	W111 D109	W112 D110	W113 D111	W114 D112	W115 D113	W116 D114	W117 D115	W118 D116	W119 D117	W120 D118	W121 D119	W122 D120	W123 D121	W124 D122	W125 D123	W126 D124	W127 D125	W128 D126	W129 D127	W130 D128	W131 D129	W132 D130	W133 D131	W134 D132	W135 D133	W136 D134	W137 D135	W138 D136	W139 D137	W140 D138	W141 D139	W142 D140	W143 D141	W144 D142	W145 D143	W146 D144	W147 D145	W148 D146	W149 D147	W150 D148	W151 D149	W152 D150	W153 D151	W154 D152	W155 D153	W156 D154	W157 D155	W158 D156	W159 D157	W160 D158	W161 D159	W162 D160	W163 D161	W164 D162	W165 D163	W166 D164	W167 D165	W168 D166	W169 D167	W170 D168	W171 D169	W172 D170	W173 D171	W174 D172	W175 D173	W176 D174	W177 D175	W178 D176	W179 D177	W180 D178	W181 D179	W182 D180	W183 D181	W184 D182	W185 D183	W186 D184	W187 D185	W188 D186	W189 D187	W190 D188	W191 D189	W192 D190	W193 D191	W194 D192	W195 D193	W196 D194	W197 D195	W198 D196	W199 D197	W200 D198	W201 D199	W202 D200	W203 D201	W204 D202	W205 D203	W206 D204	W207 D205	W208 D206	W209 D207	W210 D208	W211 D209	W212 D210	W213 D211	W214 D212	W215 D213	W216 D214	W217 D215	W218 D216	W219 D217	W220 D218	W221 D219	W222 D220	W223 D221	W224 D222	W225 D223	W226 D224	W227 D225	W228 D226	W229 D227	W230 D228	W231 D229	W232 D230	W233 D231	W234 D232	W235 D233	W236 D234	W237 D235	W238 D236	W239 D237	W240 D238	W241 D239	W242 D240	W243 D241	W244 D242	W245 D243	W246 D244	W247 D245	W248 D246	W249 D247	W250 D248	W251 D249	W252 D250	W253 D251	W254 D252	W255 D253	W256 D254	W257 D255	W258 D256	W259 D257	W260 D258	W261 D259	W262 D260	W263 D261	W264 D262	W265 D263	W266 D264	W267 D265	W268 D266	W269 D267	W270 D268	W271 D269	W272 D270	W273 D271	W274 D272	W275 D273	W276 D274	W277 D275	W278 D276	W279 D277	W280 D278	W281 D279	W282 D280	W283 D281	W284 D282	W285 D283	W286 D284	W287 D285	W288 D286	W289 D287	W290 D288	W291 D289	W292 D290	W293 D291	W294 D292	W295 D293	W296 D294	W297 D295	W298 D296	W299 D297	W300 D298	W301 D299	W302 D300	W303 D301	W304 D302	W305 D303	W306 D304	W307 D305	W308 D306	W309 D307	W310 D308	W311 D309	W312 D310	W313 D311	W314 D312	W315 D313	W316 D314	W317 D315	W318 D316	W319 D317	W320 D318	W321 D319	W322 D320	W323 D321	W324 D322	W325 D323	W326 D324	W327 D325	W328 D326	W329 D327	W330 D328	W331 D329	W332 D330	W333 D331	W334 D332	W335 D333	W336 D334	W337 D335	W338 D336	W339 D337	W340 D338	W341 D339	W342 D340	W343 D341	W344 D342	W345 D343	W346 D344	W347 D345	W348 D346	W349 D347	W350 D348	W351 D349	W352 D350	W353 D351	W354 D352	W355 D353	W356 D354	W357 D355	W358 D356	W359 D357	W360 D358	W361 D359	W362 D360	W363 D361	W364 D362	W365 D363	W366 D364	W367 D365	W368 D366	W369 D367	W370 D368	W371 D369	W372 D370	W373 D371	W374 D372	W375 D373	W376 D374	W377 D375	W378 D376	W379 D377	W380 D378	W381 D379	W382 D380	W383 D381	W384 D382	W385 D383	W386 D384	W387 D385	W388 D386	W389 D387	W390 D388	W391 D389	W392 D390	W393 D391	W394 D392	W395 D393	W396 D394	W397 D395	W398 D396	W399 D397	W400 D398	W401 D399	W402 D400	W403 D401	W404 D402	W405 D403	W406 D404	W407 D405	W408 D406	W409 D407	W410 D408	W411 D409	W412 D410	W413 D411	W414 D412	W415 D413	W416 D414	W417 D415	W418 D416	W419 D417	W420 D418	W421 D419	W422 D420	W423 D421	W424 D422	W425 D423	W426 D424	W427 D425	W428 D426	W429 D427	W430 D428	W431 D429	W432 D430	W433 D431	W434 D432	W435 D433	W436 D434	W437 D435	W438 D436	W439 D437	W440 D438	W441 D439	W442 D440	W443 D441	W444 D442	W445 D443	W446 D444	W447 D445	W448 D446	W449 D447	W450 D448	W451 D449	W452 D450	W453 D451	W454 D452	W455 D453	W456 D454	W457 D455	W458 D456	W459 D457	W460 D458	W461 D459	W462 D460	W463 D461	W464 D462	W465 D463	W466 D464	W467 D465	W468 D466	W469 D467	W470 D468	W471 D469	W472 D470	W473 D471	W474 D472	W475 D473	W476 D474	W477 D475	W478 D476	W479 D477	W480 D478	W481 D479	W482 D480	W483 D481	W484 D482	W485 D483	W486 D484	W487 D485	W488 D486	W489 D487	W490 D488	W491 D489	W492 D490	W493 D491	W494 D492	W495 D493	W496 D494	W497 D495	W498 D496	W499 D497	W500 D498	W501 D499	W502 D500	W503 D501	W504 D502	W505 D503	W506 D504	W507 D505	W508 D506	W509 D507	W510 D508	W511 D509	W512 D510	W513 D511	W514 D512	W515 D513	W516 D514	W517 D515	W518 D516	W519 D517	W520 D518	W521 D519	W522 D520	W523 D521	W524 D522	W525 D523	W526 D524	W527 D525	W528 D526	W529 D527	W530 D528	W531 D529	W532 D530	W533 D531	W534 D532	W535 D533	W536 D534	W537 D535	W538 D536	W539 D537	W540 D538	W541 D539	W542 D540	W543 D541	W544 D542	W545 D543	W546 D544	W547 D545	W548 D546	W549 D547	W550 D548	W551 D549	W552 D550	W553 D551	W554 D552	W555 D553	W556 D554	W557 D555	W558 D556	W559 D557	W560 D558	W561 D559	W562 D560	W563 D561	W564 D562	W565 D563	W566 D564	W567 D565	W568 D566	W569 D567	W570 D568	W571 D569	W572 D570	W573 D571	W574 D572	W575 D573	W576 D574	W577 D575	W578 D576	W579 D577	W580 D578	W581 D579	W582 D580	W583 D581	W584 D582	W585 D583	W586 D584	W587 D585	W588 D586	W589 D587	W590 D588	W591 D589	W592 D590	W593 D591	W594 D592	W595 D593	W596 D594	W597 D595	W598 D596	W599 D597	W600 D598	W601 D599	W602 D600	W603 D601	W604 D602	W605 D603	W606 D604	W607 D605	W608 D606	W609 D607	W610 D608	W611 D609	W612 D610	W613 D611	W614 D612	W615 D613	W616 D614	W617 D615	W618 D616	W619 D617	W620 D618	W621 D619	W622 D620	W623 D621	W624 D622	W625 D623	W626 D624	W627 D625	W628 D626	W629 D627	W630 D628	W631 D629	W632 D630	W633 D631	W634 D632	W635 D633	W636 D634	W637 D635	W638 D636	W639 D637	W640 D638	W641 D639	W642 D640	W643 D641	W644 D642	W645 D643	W646 D644	W647 D645	W648 D646	W649 D647	W650 D648	W651 D649	W652 D650	W653 D651	W654 D652	W655 D653	W656 D654	W657 D655	W658 D656	W659 D657	W660 D658	W661 D659	W662 D660	W663 D661	W664 D662	W665 D663	W666 D664	W667 D665	W668 D666	W669 D667	W670 D668	W671 D669	W672 D670	W673 D671	W674 D672	W675 D673	W676 D674	W677 D675	W678 D676	W679 D677	W680 D678	W681 D679	W682 D680	W683 D681	W684 D682	W685 D683	W686 D684	W687 D685	W688 D686	W689 D687	W690 D688	W691 D689	W692 D690	W693 D691	W694 D692	W695 D693	W696 D694	W697 D695	W698 D696	W699 D697	W700 D698	W701 D699	W702 D700	W703 D701	W704 D702	W705 D703	W706 D704	W707 D705	W708 D706	W709 D707	W710 D708	W711 D709	W712 D710	W713 D711	W714 D712	W715 D713	W716 D714	W717 D715	W718 D716	W719 D717	W720 D718	W721 D719	W722 D720	W723 D721	W724 D722	W725 D723	W726 D724	W727 D725	W728 D726	W729 D727	W730 D728	W731 D729	W732 D730	W733 D731	W734 D732	W735 D733	W736 D734	W737 D735	W738 D736	W739 D737	W740 D738	W741 D739	W742 D740	W743 D741	W744 D742	W745 D743	W746 D744	W747 D745	W748 D746	W749 D747	W750 D748	W751 D749	W752 D750	W753 D751	W754 D752	W755 D753	W756 D754	W757 D755	W758 D756	W759 D757	W760 D758	W761 D759	W762 D760	W763 D761	W764 D762	W765 D763	W766 D764	W767 D765	W768 D766	W769 D767	W770 D768	W771 D769	W772 D770	W773 D771	W774 D772	W775 D773	W776 D774	W777 D775	W778 D776	W779 D777	W780 D778	W781 D779	W782 D780	W783 D781	W784 D782	W785 D783	W786 D784	W787 D785	W788 D786	W789 D787	W790 D788	W791 D789	W792 D790	W793 D791	W794 D792	W795 D793	W796 D794	W797 D795	W798 D796	W799 D797	W800 D798	W801 D799	W802 D800	W803 D801	W804 D802	W805 D803	W806 D804	W807 D805	W808 D806	W809 D807	W810 D808	W811 D809	W812 D810	W813 D811	W814 D812	W815 D813	W816 D814	W817 D815	W818 D816	W819 D817	W820 D818	W821 D819	W822 D820	W823 D821	W824 D822	W825 D823	W826 D824	W827 D825	W828 D826	W829 D827	W830 D828	W831 D829

Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of: In- and exclusion criteria

- Pre-treatment signs & symptoms
DSM-IV rules for diagnosis & efficacy
Rating Scales: HDRS-21, MADRS, HAM-A
Medical resource utilisation
Pre-trial & Concomitant medication
Drug administration
(Serious) Adverse events
Admission to the acute and extension phases
Right flow of the trial

••Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

***Entering Extension Phase: only remitters as defined by the DSM-IV criteria of efficacy

*****Q-LES-Q : Quality of Life, Enjoyment and Satisfaction Questionnaire**

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Table 4

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DAY	minus D7	D0	=>D4
TREATMENTGROUP			
Placebo (PLC)	PLC+PLC	2x(PLC+PLC)	2x(PLC+PC)
PIP - Active / Day 4	PLC+PLC	2x(PLC+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PIP - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PLC - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PLC)/d	2x(CIT (10mg)+PLC)/d

10

Table 5

[illegible]

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[illegible]

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[illegible]

[illegible]

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[illegible]

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[illegible]

[illegible]

GLOSSARY	
S-HT	= serotonin
S-HT1	= serotonin 1 receptor
S-HT1A	= serotonin 1A receptor
S-HT1B	= serotonin 1B receptor
S-HT2A/D4	= serotonin 2A and dopamine D4 receptor
S-HT2B	= serotonin 2B receptor
S-HT2C	= serotonin 2C receptor
S-HT3	= serotonin 3 receptor
S-HT6	= serotonin 6 receptor
AMPA	= alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate
CB1	= cannabinoid receptor 1
CINODs	= COX-inhibiting nitric oxide donors
COX	= cyclooxygenase
COX-2	= cyclooxygenase 2
CRF-1	= Corticotropin-Releasing Factor Receptor 1
D1	= Dopamine 1
D2	= Dopamine 2
DA	= Dopamine
ERK	= extracellular signal-related kinase
GABA	= gamma-aminobutyric acid
GABA-A	= gamma-aminobutyric acid A receptor
GABA-B	= gamma-aminobutyric acid B receptor
GPCR	= G-Protein-Coupled Receptor
GR	= glucocorticoid receptor
H3	= histamine H3-receptor
MAO	= mono-amine oxidase
MAO-A	= mono-amine oxidase A
MAO-B	= mono-amine oxidase B
MC4	= melanocortin-4 receptor
MCH	= Melanin concentrating hormone
MuR	= mu-opioid receptor
MT	= melatonin receptor
NARI	= selective nor-adrenaline re-uptake inhibitor
NaSSA	= nortriptyline-specific serotonergic antidepressant
NDRI	= selective nor-adrenaline and dopamine re-uptake inhibitor
NGF	= Nerve Growth Factor
NGF	= nerve growth factor
NK1	= neurokinin 1 receptor
NK2	= neurokinin 2 receptor
NK3	= neurokinin 3 receptor
NMDA	= N-Methyl-D-aspartate
NSAID	= Non-steroidal anti-inflammatory drugs
PDE4	= phosphodiesterase-4
RNA	= reversible inhibitor of mono-amine oxidase A
SCT-11	= G protein-coupled receptor
SDA	= Serotonin/Dopamine Antagonist
SDRI	= selective serotonin and dopamine reuptake inhibitor
SNRI	= selective serotonin, nor-adrenaline and dopamine reuptake inhibitor
SSRI	= selective serotonin and nor-adrenaline reuptake inhibitor
SSRI	= selective serotonin reuptake inhibitor
VTB	= vasopressin 1B receptor

Table 6

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[illegible]

[illegible]

[illegible]

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Monomeric Transmitter Systems	61	NSSA	Insomnia	ORG 14205	100 to 300 mg daily	Organon
Monomeric Transmitter Systems	62	NDR	Depression (bipolar disorder)	GW333367	10 to 60 mg daily	GlaxoSmithKline
Monomeric Transmitter Systems	63	Neurotransmitter Inhibitor	Parkinson's Disease	GW333367	10 to 60 mg daily	GlaxoSmithKline
Monomeric Transmitter Systems	64	Neurotransmitter Inhibitor	Parkinson's Disease	GW333367	10 to 60 mg daily	GlaxoSmithKline
Monomeric Transmitter Systems	65	Neurotransmitter Inhibitor	Schizophrenia	SR 48692	10 to 300 mg daily	Sandoz Pharma
Monomeric Transmitter Systems	66	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	67	Neurotransmitter Inhibitor	Anxiety	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	68	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	69	Neurotransmitter Inhibitor	Depression / Anxiety	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	70	Neurotransmitter Inhibitor	Schizophrenia	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	71	Neurotransmitter Inhibitor	Schizophrenia / BSS / Overactive bladder	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	72	Neurotransmitter Inhibitor	Anxiety	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	73	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	74	Neurotransmitter Inhibitor	Depression	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	75	Neurotransmitter Inhibitor	Pain	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	76	Neurotransmitter Inhibitor	Depression	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	77	Neurotransmitter Inhibitor	Pain	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	78	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	79	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	80	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	81	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	82	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	83	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	84	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	85	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	86	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	87	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	88	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	89	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	90	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	91	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	92	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	93	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	94	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	95	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	96	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	97	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	98	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	99	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma
Excitatory Amino Acid System	100	Neurotransmitter Inhibitor	Alzheimer's Disease	SR 48692	10 to 300 mg daily	Sandoz Pharma

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Monomimetic Transmitter Systems	83	5HT-1f modulation	Depression	SNEC-2		Synapse
	84	SDA	Schizophrenia	Quetiapine		AsaZentica
		SDA	Schizophrenia	Ziprasidone		Bristol-Myers Squibb
		SDA	Schizophrenia	Ziprasidone		Johnson & Johnson Pharmaceutical
		SDA	Schizophrenia	Ziprasidone		Kraft/BASF
		SDA	Schizophrenia	Ziprasidone		Lilly
		SDA	Schizophrenia	Ziprasidone		Novartis Pharmaceuticals
		SDA	Schizophrenia	Ziprasidone		Pfizer
		SDA	Schizophrenia	Ziprasidone		Sunovion
		SDA	Schizophrenia	Ziprasidone		Amnion Pharmaceuticals
		SDA	Schizophrenia	Ziprasidone		Amnion Pharmaceuticals
		SDA	Schizophrenia	Ziprasidone		Amnion Pharmaceuticals
		SDA	Schizophrenia	Ziprasidone		Amnion Pharmaceuticals
		SDA	Schizophrenia	Ziprasidone		Amnion Pharmaceuticals
		SDA	Schizophrenia	Ziprasidone		Amnion Pharmaceuticals
Monomimetic Transmitter Systems	85	SDRI	Depression / Anxiety	S-1627		Serie
	86	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	87	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	88	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	89	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	90	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	91	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	92	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	93	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	94	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	95	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	96	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	97	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	98	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
	99	Second messenger beta agonist	Depression / Anxiety	S-1627		Serie
Monomimetic Transmitter Systems	100	SDRI	Depression / Anxiety	S-1627		Serie
	101	SDRI	Depression / Anxiety	S-1627		Serie
	102	SDRI	Depression / Anxiety	S-1627		Serie
	103	SDRI	Depression / Anxiety	S-1627		Serie
	104	SDRI	Depression / Anxiety	S-1627		Serie
	105	SDRI	Depression / Anxiety	S-1627		Serie
	106	SDRI	Depression / Anxiety	S-1627		Serie
	107	SDRI	Depression / Anxiety	S-1627		Serie
	108	SDRI	Depression / Anxiety	S-1627		Serie
	109	SDRI	Depression / Anxiety	S-1627		Serie
	110	SDRI	Depression / Anxiety	S-1627		Serie
	111	SDRI	Depression / Anxiety	S-1627		Serie
	112	SDRI	Depression / Anxiety	S-1627		Serie
	113	SDRI	Depression / Anxiety	S-1627		Serie
	114	SDRI	Depression / Anxiety	S-1627		Serie

PHARMAC. GROUP (see overview hereunder)	nr. PH. PROF.	PHARMACOLOGICAL PROFILE	MAIN INDICATIONS	COMPOUND	DOSE RANGE	COMPANY
Noncatecholamine Transmitter Systems	97	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	98	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	99	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	100	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	101	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	102	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	103	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	104	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	105	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	106	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	107	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	108	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	109	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	110	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	111	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	112	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	113	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	114	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	115	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	116	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
Amino Acid Transmitter Systems	117	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	118	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	119	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	120	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	121	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	122	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	123	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	124	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	125	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	126	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	127	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	128	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	129	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	130	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	131	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	132	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	133	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	134	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	135	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	136	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
PHARMACOLOGICAL GROUPS: COMPOUNDS WORKING ON THE	137	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	138	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	139	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	140	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	141	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	142	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	143	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	144	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	145	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	146	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	147	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	148	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	149	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	150	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	151	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	152	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent
	153	SSRI	Depression / Anxiety	Paroxetine	20 to 60 mg daily	GlaxoSmithKline
	154	SSRI	Depression / Anxiety	Fluoxetine	10 to 60 mg daily	Lundbeck / Forest Laboratories
	155	SSRI	Depression / Anxiety	Escitalopram	10 to 30 mg daily	off patent
	156	SSRI	Depression / Anxiety	Desipramine	10 to 30 mg daily	off patent

Examples

Example 1: Measuring pKi values of test compounds

5 In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor. The affinity of test compounds for the respective receptors has been performed according to conventional procedures known in the art.

An indication "0" means that no affinity has been measured between the test compound and the receptor.

10 The columns displaying the pKi values for the D4 and the 5-HT2A receptor are filled with dark grey. pKi values between 8 and 9 and higher than 9 are represented by light grey boxes.

15 Example 2: Foregoing pipamperon-citalopram treatment in major depressive disorder: a placebo and active controlled period finding clinical trial

Table 2 represents the set-up of a clinical trial comprising for treatment groups:

Group Plc – Active / Day 0 represents the group receiving 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the mono therapy.

20 Group Pip - Active / Day 0 represents the group receiving a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the non-foregoing combo therapy.

25 Group Pip - Active / Day 4 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the fifth (Day 4) day of active treatment in the clinical trial. This administration regime is also indicated as the foregoing therapy with combination therapy starting after 4 days of active treatment.

30 Group Pip - Active / Day 7 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the eight (Day 7) day of active treatment in the clinical trial. This administration regime is also

indicated as the foregoing therapy with combination therapy starting after 7 days of active treatment.

All subjects also undergo a placebo (PLC) run-in therapy, administered during a period of about 7 days before the active treatment starts.

5 During daily (D), weekly (W) or monthly (M) visits, several parameters are measured.

Under NECT is to be understood: Neuronal E-clinical Trial = Vesalius Expert development for this trial which includes the bottom-up measurement of:

- In- and exclusion-criteria
- Functional status evaluation
- 10 - Medical history
- (Pre-)treatment signs & symptoms
- DSM-IV rules for diagnosis & efficacy
- HDRS-28 (Hamilton Depression Rating Scale - 28 items)
- Medical resource utilisation
- 15 - Pre-trial & Concomittant medication
- Drug administration
- (Serious) Adverse events
- Admission to the acute and extension phase of treatment
- Right flow of the trial
- 20

Example 3: combo pipamperon-citalopram: therapeutic use in Major Depression

25 Purpose

Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl][1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to patients in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the antidepressant effect of the selective serotonin re-uptake inhibitor
 30 citalopram. Preferably, pipamperon is administered daily at least 4-5 days before administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi
 35 value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopram in the treatment of patients with major depression.

Details

- Design:** Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient practice but without concomitant use of mood enhancing drugs, open label
- Control:** No
- Phase:** Phase IIa – preliminary Proof of Concept
- Location:** Belgium – Research Centre ANIMA, Alken
- End Points :** Assessment scale scores, Hamilton Depression Rating Scale 17 items, Reduction, Response, Remission
- Medication:** Exclusion of mood stabilisers, antipsychotics (typical and atypical) and other antidepressants

Subjects

Type	No.	Sex	Age
Patients	23	10 male & 13 female	23-80 (mean 47) years

- 5 **Characteristics:** patients had a major depressive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

Treatments

- 10 **PIP-CIT¹ add-on:** citalopram from day minus 60-20 – pipamperon from DAY 0

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon ¹ Citalopram ¹	+ Pip.: 8-12 mg/day – Cit.: 20-40 mg/day	PO	bid	8 weeks

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

15

PIP-CIT¹ fore-going 1-5: pipamperon from day 0 – cital from day 1-5

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon ¹ Citalopram ¹	+ Pip.: 8-12 mg/day – Cit.: 20-40 mg/day	PO	bid	8 weeks

- 20 1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT¹ fore-going 6-8: pipamperon from day 0 – citalopram from day 6-8

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon ¹ Citalopram ¹	+ Pip.: 8-12 mg/day – Cit.: 20-40 mg/day	PO	bid	8 weeks

- 5 1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

Results

	PIP-CIT add-on	PIP-CIT foregoing	
	After 20-60 DAYS (mean 33) (n = 5)	1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Mean Used Medication			
Pipamperone	9mg/day	10mg/day	11mg/day
Citalopram	30mg/day	26mg/day	30mg/day
Depression scale scores			
HDRS 17-item total score			
baseline	29	23	28
endpoint (week 8)	4	5	11
diminishment at week 8	-25 (+8/-9)	-18 (+8/-8)	-17 (+17/-17)
% reduction at week 8	86 (+14/-12)	80 (+20/-30)	61 (+39/-61)
response ¹ at week 8	5 (100%)	15 (100%)	2 (67%)
remission ² at week 8	4 (80%)	10 (67%)	1 (33%)

- 10 1. Response = $\geq 50\%$ reduction in HDRS 17-item score;
2. Remission = HDRS 17-item score < 8

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

15

Add-on PIP-CIT

Figure 1 schematically depicts the "add-on" treatment with pipamperon 8-12 (mean 9) mg (bid) after treatment with citalopram 10-20 (mean 30) mg (bid) during 20-60 (mean 33)

days (PIPCIT ADD-ON) with HDRS-17. Totalscore is 29 at baseline in MDD in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 5 2000).

Figure 2 schematically depicts the HDRS-17 change from baseline in the combo pipamperon as "add-on" to citalopram vs SNRI (duloxetine) in Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 3 schematically depicts the remission rates (HDRS-17 ≤ 7) with the combo pipamperon as "add-on" to citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in 15 Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase *et al.* (Br. J. Psychiatry (2001) 178:234-241). Treatment with SSRIs is according to a meta-analysis of Thase *et al.* (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase *et al.* (Br. J. 20 Psychiatry (2001) 178:234-241).

Fore-going 1-5 PIP-CIT

Figure 4 schematically depicts the "fore-going" treatment during 1-5 (mean 4) days with pipamperon 8-12 (mean 10) mg (bid), followed with the combination treatment of 25 pipamperon and citalopram 20-50 (mean 26) mg/day (bid) (PIPCIT FG 1-5) in MDD (HDRS-17 at BL = 23) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

30 Figure 5 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 10 mg/day) (bid) 1-5 (mean 4) days 35 before treatment with SSRI (n=15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 6 schematically depicts the remission rates (HDRS-17 ≤ 7) with the combo pipamperon with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (venlafaxine) in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n=5). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with SSRIs is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).

Fore-going 6-8 PIP-CIT

Figure 7 schematically depicts the "fore-going" treatment during 6-8 (mean 7) days with pipamperon 8-12 (mean 11) mg/day (bid), followed with the combination treatment of pipamperon and citalopram 20-40 (mean 30) mg/day (bid) (PIPCIT FG 6-8) in MDD (HDRS-17 at BL = 28) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 8 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 7 days with pipamperon (11 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 11 mg/day) (bid) 6-8 (mean 7) days before treatment with SSRI (n=3). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Comparison "add-on" vs "fore-going"

Figure 9 schematically depicts a comparison between "fore-going" and "add-on" treatments with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in MDD in comparison with the standard efficacy of antidepressants in clinical trials according to Khan *et al.* (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 10 schematically depicts a comparison between "fore-going" and "add-on" treatments. In particular, the HDRS-17 change from baseline between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI duloxetine in Major Depression is depicted. Treatment with the combo pipamperon as "add-on" to citalopram, with pipamperon 8-12 mg/day (mean 9 mg/day) 20-60 (mean 33) days after treatment with the SSRI (n=5). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 11 mg/day; bid) 6-8 days (mean 7 days) before treatment with the SSRI (n = 15). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 10 mg/day; bid) 1-5 days (mean 4 days) before treatment with the SSRI (n = 15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein *et al.*, (Clin. Psychiatry, in press).

Figure 11 schematically depicts the remission rates (HDRS-17 ≤ 7) in a comparison between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI venlafaxine in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n = 15). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase *et al.* (Br. J. Psychiatry (2001) 178:234-241). Treatment with pipamperon as "add-on" to citalopram, with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n = 5).

The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according HDRS 17-item in all the treatment groups. This was especially true for the 'add-on' group probably caused by the longer treatment with an active antidepressant (+33 days). The huge therapeutic effect observed in the 'PIP-CIT 1-5' group present for at a mean dosage of pipamperon of 10 mg per day and administered the first four days of treatment without an active antidepressant, indicates the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. Only 1 patient discontinued treatment due to a lost of follow-up.

Adverse Events

Side effects (patients)	PIP-CIT add-on After 20-60 DAYS (mean 33) (n = 5)	PIP-CIT foregoing 1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Discontinued treatment due to adverse events	0	0	0
By system:			
body as a whole	0	0	0
central and peripheral nervous system	1(20%)	4(26.6%)	0
gastrointestinal	1(20%)	5(33%)	2(66.6%)
musculoskeletal	1(20%)	3(20%)	0
psychiatric	0	0	0
respiratory	0	1(6.6%)	0
skin and appendages	1(20%)	2(13.3%)	1(33.3%)
vascular	0	1(6.6%)	0
urinary	0	1(6.6%)	0

Laboratory parameters, ECG, bodyweight and vital signs were not measured since this was a naturalistic study.

5

AssessmentOutcome

Efficacy: the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is comparable to the add-on combo pipamperon-citalopram.

- 10 **Efficacy:** the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the 7-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day.

Efficacy: the combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the in the art known antidepressants SSRIs.

15

Tolerability

Tolerability: the 4-day fore-going treatment is comparable to the 7-day fore-going combo is comparable to add-on combo pipamperon-citalopram.

Tolerability: no discontinued treatment due to adverse events.

5

Study Messages

The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and '4-day fore-going' combo 'pipamperon 8 -12 mg/d - citalopram 20 - 40 mg/day' is in this study as twice higher as
10 known in the art in the treatment of patients with major depression.

The combo pipamperon-citalopram is generally well tolerated in patients with depression i.e. at least no specific added adverse events were occurring by adding pipamperon at the doses used in the study.

15

Example 4: combo pipamperon-citalopram: therapeutic use in Obsessive-Compulsive Disorder (OCD).

Purpose

- 5 Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl][1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to a patient in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the effect of the selective serotonin re-uptake inhibitor citalopram towards OCD. Preferably, pipamperon is administered daily at least 4-5 days before
10 administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards
15 other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopram in the treatment of patients with OCD.

Details

- Design: Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient practice but without concomitant use of mood enhancing drugs, open label
- Control: No
- Phase: Phase IIa – preliminary Proof of Concept
- Location: Belgium – Research Centre ANIMA, Alken
- End Points : Assessment scale scores, Yale-Brown Obsessive-Compulsive Scale, Reduction, Remission
- Medication: Exclusion of mood stabilisers, antipsychotics (typical and atypical) and other antidepressants

20

Subjects

Type	No.	Sex	Age
Patients	7	1 male & 7 female	20-63 (mean 33) years

Characteristics: patients had an obsessive-compulsive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

5 Treatments

PIP-CIT¹ ADD-ON: citalopram from DAY minus 730-60 – pipamperon from DAY 0

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperone ¹	+ Pip.: 8-16 mg/day – Cit.: 30-80	PO	bid	12
Citalopram ¹	mg/day			weeks

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical response.

10

PIP-CIT¹ FORE-GOING 4-6: pipamperon from DAY 0 – citalopram from DAY 4-6

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperone ¹	+ Pip.: 8-16 mg/day – Cit.: 30-80	PO	bid	12
Citalopram ¹	mg/day			weeks

15

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical response.

Results

PIP-CIT add-on	
after 730-60 DAYS (mean 241) (n = 6)	
with mean Cit. 54mg/d and Pip. 11mg/d	
PIP-CIT foregoing	
4-6 DAYS (mean 5) (n = 2)	
with mean Cit. 60mg/d and Pip. 10mg/d	
Y-BOCS score	
<u>Baseline</u>	
Total	31
Obsessions	18
Compulsions	13
Endpoint (week 12)	
<u>Total</u>	<u>15</u>
diminishment	-16 (+16/-11)
% reduction	53
<u>Obsessions</u>	
total	8
diminishment	-10 (+9/-7)
% reduction	57
<u>Compulsions</u>	
total	7
diminishment	-6 (+7/-6)
% reduction	45
<u>% Remission</u>	
YBOCS score ≤8	29
BOCS score ≤16	57

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

Figure 12 schematically depicts the Y-BOCS total score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-

citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

5 Figure 13 schematically depicts the Y-BOCS obsession score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

10 Figure 14 schematically depicts the Y-BOCS compulsion score: "fore-going" and "add-on" treatment with pipamperon (8-16 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram (n = 7). Treatment with fluvoxamine (controlled release) mean 271 mg/day (n = 253) is according to Hollander et al. (2003).

15 The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according Y-BOCS total score, obsession and compulsion scores. This indicates the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. No patient discontinued treatment.

20

Assessment

Efficacy: the combo pipamperone 8-16mg/d - citalopram 30-80mg/day > the in the art known compounds effective towards OCD (Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry 64: 640-647, Jun 2003 Mount Sinai School of Medicine, New York, New York, USA; Solvay Pharmaceuticals Inc., Marietta, Georgia, USA).

25

Study Messages

30 The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and 'fore-going' combo 'pipamperon 8-15 mg/d - citalopram 30-80 mg/day' is in this study as twice higher as known in the art in the treatment of patients with obsessive-compulsive disorder.

35

Example 5: combo pipamperon-citalopram: therapeutic use in Panic Disorder.**Purpose**

Preliminary examination of a "fore-going" and "add-on" treatment with pipamperon and
5 citalopram in comparison with the SSRI in Panic Disorder.

Results

The results are indicated in Figure 15. Figure 15 schematically depicts the CGI-severity
score: "fore-going" and "add-on" treatment with pipamperon (8 mg/day; bid) and
10 citalopram (20-40 mg/day; bid) in comparison with the SSRI in Panic Disorder. Treatment
with the combo pipamperon-citalopram (n = 3). Treatment with paroxetine is according to
the Journal of Clinical Psychiatry (2004) 65: 405-413. Treatment with Sertraline is
according to the Journal of Clinical Psychiatry (2004) 65: 405-413.

15 Conclusion

Notably, although a small test group has been used (n = 3), the distribution around the
mean is good. It will further be apparent from Figure 15 that the effect of the combo
treatment of pipamperon and citalopram is twice as high as the standard treatments with
paroxetine or sertraline.

20

Example 6: POC process for mayor depressive disorder

Concept: Combo of the high selective 5-HT_{2A/D4} antagonist pipamperon with:

- 25 - a compound active towards the Amino Acid Transmitter, Peptidergic Transmitter,
Adenosine Transmitter, Endocrine and/ or Enzymatic System;
- a fore-going admission during 4 days of pipamperon;
- a dose of pipamperon of 12 mg/day

30 Objectives: Demonstrating that this combo therapy has:

- the potency of being a treatment standard for depression by having an added value of
reducing the total score of the Hamilton Depression Rating Scale – 17 items (HDRS-
17) after 8 weeks of therapy with a least 20% more than reached with the conventional
known antidepressants, *i.e.* 60% versus 40%. This stands for an added medium
35 demission of 5 points on the total score of the HDRS-17 and by this will be very highly

significant since the mean difference in all recent clinical trials between placebo and active treatment is 2.5;

- a more sustained therapeutic effect than the conventional mono therapy by preventing significant more relapses during 48 weeks following the acute treatment; and/or
- 5 - a complete neutral safety profile, e.g. there are no more adverse events in the combo therapy than in mono admission of the in the combo used antidepressant compound.

Process: the following different steps were implemented to reach out for these objectives (see also Tables 3 and 4):

- 10 (1) an naturalistic open label study ($n \geq 20$) on a depressive population with a normal variability of medical and psychiatric history, course of depression, earlier and concomitant therapy admitting the golden standard antidepressant citalopram 20-40 mg/day and a dose of 8-12 mg/day of pipamperon in a foregoing, simultaneous or add-on use.

- 15 (2) a 16 weeks placebo controlled randomised four armed study of each 36 patients with a major depressive disorder admitting:
 - from day 0: placebo or pipamperon (PIP) 10 mg/day or an active antidepressant compound or the combination of the last two;
 - from day 4: placebo or pipamperon 10 mg/day combined with an active antidepressant compound or an active antidepressant compound without pipamperon.

By including rigorous control groups (placebo and active comparator; see Tables 3 and 4) this clinical trial is evaluated as a proof of concept of the added value of the combo and the foregoing treatment method since the inclusion/exclusion of:

- 25 - a negative trial, i.e. no significant difference between the placebo and active treatment with the comparator;
- a failed trial, i.e. no significant difference between the active and the studied treatment i.e. the combo.

- (3) an active controlled randomised relapse prevention study following the POC trial
 - 30 during another 36 weeks with three arms of each 36 patients which is formed by:
 - continuation of the active mono therapy;
 - randomising the patients with a combo therapy in a group with an active mono therapy and with a continuation of the combo treatment.

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